

Ramon Andrade De Mello  
Giannis Mountzios · Álvaro A. Tavares  
*Editors*

# International Manual of Oncology Practice

iMOP - Principles of Oncology

*Second Edition*

 Springer

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# Preface

Dear colleague,

Nowadays, cancer is a serious disease which presents normally with a high mortality and important treatment sequels. The clinical approach of the cancer patients is really a challenge for the physicians, nurses, psychologists, and all subjects involved, namely, the patients and their family. Fortunately, the cancer sciences currently had been developing several strategies to overcome this issue: personalizing medicine, predictive and prognostic biomarkers, novel target therapies, and also innovative supportive therapies. Thus, the oncological treatment is a multimodal process which involves a comprehensive approach. More recently, the most important medical oncology societies are important key institutions to disseminate knowledge and establish clinical practice guidelines for the patient's care. Also, they focus in an intensive task force to create a good and solid network education platform for young and senior medical oncologists' updating. Nevertheless, medical oncology training directors and the national board examination council worldwide concurrently work to try to adapt the novel evidence to their reality and clinical practice. Taking into account all these paramount features, the 2nd edition of the *International Manual of Oncology Practice* working group had developed and updated a very comprehensive and evidence-based book to help the clinicians worldwide integrate the knowledge fit to their clinical practice. Experts from Europe, North America, Latin America, Asia, Middle East, and Africa had established a solid and well-developed network platform to share experiences and write a consistent evidence-based book for the global oncology community, according to their local economical and sociocultural concerns. We hope you enjoy our work.

São Paulo, Brazil

Sincerely yours,  
Professor Ramon Andrade De Mello  
On behalf of all authors and editors

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## About the Editors

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He completed specialization in medicine and molecular oncology and his PhD in molecular oncology (lung cancer) at the Faculty of Medicine, University of Porto, Portugal. He also completed the medical oncology training at Portuguese Oncology Institute, Porto, Portugal, supported by the ACSS, Ministry of Health, Lisbon, Portugal, and a clinical research fellowship in lung cancer clinical trials at the Lung Unit, Royal Marsden NHS Foundation Trust, Chelsea, London, UK, supported by the ESMO. He is Fellow Member of the American College of Physicians.

He was consultant medical oncologist at the Edinburgh Cancer Center, Western General Hospital, Edinburgh, UK. Currently, he is also professor of Medical Oncology at the School of Medicine, University of Algarve, Faro, Portugal, since 2013 and Federal University of São Paulo, Brazil, since 2019. Furthermore, he is honorary professor of Medicine at the University of Porto since 2010. Professor De Mello performs both basic and clinical research on biomarkers, GI cancer, and lung cancer; further, he has an active office working in medical oncology.

He is editor of three books (*Tamoxifen Concepts and Cancer: New Paradigms; Vimentin Concepts and Molecular Mechanisms*, Nova Science, NY, USA, 2013; and *International Manual of Oncology Practice*, Springer, Switzerland, First Edition in 2015 and Second Edition in 2019) and author of several scientific articles, chapters, and comments on basic and clinical research. He presented more than 50 papers in congresses and conferences in several countries, such as the USA, Sweden, Denmark, Brazil, China, Bulgaria, Portugal, and Spain. Furthermore, he serves on the editorial board of several reputed scientific journals, such as *PLOS One*, *Rare Tumors*, and *Oncology Reviews*, and he is also a scientific reviewer of the *British Journal of Cancer*, *Journal of Thoracic Oncology*, *Annals of Internal Medicine*, and

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Prof. De Mello is member of the ASCO Cancer Educational Committee 2016–2019 (Upper GI Tumors) and ESMO Gastrointestinal Faculty (ESMO Educational Committee) 2018–2022.

**Giannis Mountzios** was born in Larissa, Greece, in 1974. He obtained his medical degree (MD) from the Aristotle University of Thessaloniki in 1998 with a scholarship from the Greek Ministry of Education and graduated from the Hellenic Military Medical Academy the same year. He completed his residency in Internal Medicine at the Air Force General Hospital of Athens and in Medical Oncology at the University of Athens School of Medicine, Alexandra University Hospital (Pr. M. A. Dimopoulos). He then obtained a master's (MSc) in Translational and Clinical Research in Oncology from the Institut Gustave Roussy and the University Paris XI (Paris-Sud), France, in 2007 (Pr. Jean-Charles Soria) and became board-specified in Medical Oncology in 2009. In 2010, he obtained his PhD in Medical Oncology from the University of Athens School of Medicine. He is currently working as a consultant medical oncologist at the Henry Dunant Hospital Center, Athens, Greece. He has received fellowships from the American Society of Clinical Oncology (Young Investigator Award), the European Society for Medical Oncology (Annual Fellowship for Translational Research in 2005 and Annual Fellowship for Clinical Research in 2009), and the Hellenic Society of Medical Oncology (HESMO). He is currently the general secretary of the board of directors of HESMO, former chair of the HESMO Young Medical Oncologists Committee, and former member of the Steering Committee of the Young Medical Oncologists of the ESMO.

**Álvaro A. Tavares** born in 1964, obtained his degree in Biochemistry from the University of Lisbon, Portugal. He later obtained his MSc in Molecular Biology from the New University of Lisbon and his PhD in Biomedical Sciences from the University of Porto, Portugal. He then moved to Scotland where for 5 years he was a postdoctoral at the Department of Anatomy and Physiology of the University of Dundee. In 1999, having been appointed professor at the Instituto Superior Técnico, Lisbon, he started his own research group at the Gulbenkian Science Institute. In 2009, he moved to the University of Algarve, to the newly formed Department of Biomedical Sciences and Medicine, where he currently directs the Cell Division and Cancer Biology Research Group.

In the course of his research career, he has studied proteolytic systems in rat liver mitochondria, proteolysis regulation in differentiation in the plant *Lupinus albus*, genetic regulation and expression in yeast *S. cerevisiae*, and molecular and genetic characterization of genes required for cell proliferation in *Drosophila melanogaster*. The underlying theme behind the current work of his laboratory is the basic biology of mitotic cell division, in particular the aspects regulating the formation of a bipolar mitotic spindle and the connection between centrosomes and cytokinesis.

The ultimate goal is to understand how modifications of these processes contribute to the transformation of normal cells into cancer cells. These problems are approached through a combination of biochemical, genetic, and cytological techniques, taking advantage of *Drosophila melanogaster* genetics and human tissue-cultured cells.

# **Part I**

## **Introduction**

# Chapter 1

## Cancer Epidemiology and Screening



**Gustavo Trautman Stock, Pedro Nazareth Aguiar Jr., Hakaru Tadokoro,  
and Ramon Andrade De Mello**

**Abstract** The world is facing an increase in the cancer incidence and mortality, making malignant neoplasms one of the leading causes of death worldwide. This increasing trend is predicted to continue in the next decades, with an estimated >23 million new cases and 13 million deaths caused by cancer by 2030. Excluding non-melanoma skin cancer, lung, breast, colorectal, prostate, and stomach cancers are the most common, while lung, liver, stomach, colorectal, breast, and esophageal cancers have the highest mortality rate. The prevalence of cancer in developed countries is >two-fold that in developing countries, however, cancer rates are expected to rise among developing countries, because of the ageing, population growth, and the adoption of unhealthy western lifestyle habits. Delivering high quality cancer care at an affordable cost is one of the main challenges for health care professionals and policy makers. The global cost of cancer in 2008 due to premature death and disability, excluding direct medical costs, was estimated at \$895 billion in the United States. Measures to reduce the incidence of cancer include the avoidance and modification of risk factors, vaccination against oncogenic biologic agents and the early detection of risk lesions through screening programs.

**Keywords** Cancer screening · Breast cancer · Colon cancer

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## 1.1 Introduction

In the last decades, the international community has been faced with an increasing threat posed by the elevated incidence and death rates by cancer and other non-communicable diseases (NCDs) [1]. Currently, NCDs constitute the leading cause of morbidity and mortality worldwide, being recognized as a great barrier to human development and standing out as a main focus of international health discussions [2, 3]. Among the NCDs, cancer is becoming the major cause of premature deaths, surpassing cardiovascular disease, diabetes, and chronic obstructive pulmonary disease, especially in countries with a very high human development index [4].

## 1.2 Cancer Statistics

Excluding non-melanoma skin cancer, the global cancer incidence has increased from 12.7 million in 2008 to 14.1 million in 2012, and the expected trend is an increase in new cases to close to 25 million over the next two decades. The estimated number of cancer-related deaths in 2012 was 8.2 million, which is expected to increase to nearly 13 million by 2030 [5]. These estimates correspond with the age-standardized incidence and mortality rates of 182 and 102 per 100,000, respectively, with a slight predominance among men (53% and 57%, respectively) [6].

In 2012, the five most common sites of cancer diagnosed in both sexes were lung (13.0%), breast (11.9%), colorectum (9.7%), prostate (7.9%), and stomach (6.8%). Lung cancer has the highest estimated age-standardized incidence and mortality rates (34.2 and 30.0, respectively) among men. Although prostate cancer has the second highest incidence rate (31.1), its mortality rate (7.8) is considerably lower, reflecting a lower fatality rate or improved survival. Stomach, liver, and esophageal cancers have a relatively poor prognosis, and the mortality rates are close to the incidence rates (respective incidence and mortality: 17.4 and 12.7 for stomach cancer, 15.3 and 14.3 for liver cancer, and 9.0 and 7.7 for esophageal cancer). Colorectal cancer (CRC) has an incidence rate of 20.6 and a substantially lower mortality rate (10.0) [6].

Among women, breast cancer has the highest incidence rate (43.3), followed by the cancers of the colorectum (14.3), cervix (14.0), lung (13.6), corpus uteri (8.2), and stomach (7.5). The mortality rates for cancers of the lung (11.1) and stomach (5.7) are substantially close to their corresponding incidence rate, while cancers of the breast (12.9), colorectum (6.9), cervix (6.8), and corpus uteri (1.8) have a relatively lower mortality rate [6].

The estimated prevalence shows that 32.6 million people who were diagnosed with cancer in the previous 5 years were alive in 2012. Breast cancer was the most prevalent cancer with 6.3 million survivors diagnosed within the previous 5 years, followed by prostate cancer (3.9 million) and CRC (3.5 million: 1.9 million men and 1.6 million women). Because of its very poor survival, the 5-year prevalence for



lung cancer (1.9 million: 1.3 million men and 0.6 million women) was very close to the annual mortality (1.6 million) [6].

The estimated incidence rates are directly related to age. Rates for those aged 40–44 years were 150 per 100,000, which increased to >500 per 100,000 by age 60–64 years. The incidence was higher in women until about the age of 50 years, which was when the rates in men increased and became substantially higher by the age of 60 years. More cases occurred in women before the age of 50 years because of the relative earlier age of onset of cervical and breast cancers. In those aged >60 years, prostate and lung cancers in men were more frequent [6].

### 1.3 Cancer Burden

For all cancers combined, excluding non-melanoma skin cancer, in both sexes, the highest incidence rates occur in high-income countries (i.e., North America, western Europe, Japan, the Republic of Korea, Australia, and New Zealand). Intermediate rates are observed in Central and South America, Eastern Europe, and most parts of South-East Asia, and the lowest rates occur in most parts of Africa and West and South Asia [6–8].

Mortality rate variations have also been observed. Typically, in developed countries, breast, colorectal, and prostate cancers usually have a relatively good prognosis. Conversely, cancers of the liver, stomach, and esophagus are more common in developing countries, and have a significantly poorer prognosis [6–8].

About half of the cancer incidence concentrates in Asia, with 22% in China and 7% in India. A quarter of the global incidence occurs in Europe, and the remainder is observed in America and Africa. The proportional mortality distribution shows an increase in cancer-related deaths in developing countries, mainly in Asia, Africa, and Central and South America, which account for >two-thirds of the cases [9]. Since these rates are projected to increase by about 70% worldwide in the next two decades, the greatest cancer burden will unquestionably lie in developing countries, where most of the cases are diagnosed at advanced stages. In these areas, there are also great disparities in the access to cancer care and often limited or unavailable palliative care services [10, 11].

The distribution of cancer in worldwide indicates marked differences in particular tumor types. The higher rates of cervical cancer in low-income countries contrast with the reversed trend for breast cancer, which is partly due to the heterogeneity of the health care systems and the distribution of risk factors within the countries. Population-based screening programs (e.g., mammography) have the potential to artificially increase the cancer incidence [6, 10, 11].

An analysis of cancer burden according to the region and levels of HDI revealed that the epidemiologic transition, through which low- and middle-income countries are undergoing, causes a major impact that increases population growth and ageing. Moreover, economic development, trade globalization, and urbanization facilitate

the spread of risk factors such as tobacco smoking, alcohol use, an unhealthy diet, and obesity [12, 13].

In 2008, cancers of colorectum, lung, breast, and prostate were responsible for 18–50% of the total disability-adjusted life years (DALYs) worldwide. An additional burden of 25–27% from infection-related cancers (i.e., liver, stomach, and cervical) was observed in Sub-Saharan Africa and eastern Asia. Years of life lost (YLLs) was the main contributor of the DALYs overall, accounting for 93% of the total cancer burden. Developing countries had a consistently higher proportion of YLLs of the total DALYs than the developed countries [7, 14].

## 1.4 Economic Impact

Aside from the human cost, treating and caring for an increasing number of cancer patients has a huge economic impact, raising demands on the health care budgets, even in the wealthiest nations, and it poses a major threat, especially to low- and middle-income countries, and impairs public health systems and economic development.

The Global Economic Cost of Cancer report indicated that cancer has the most devastating economic impact of all the leading causes of death in the world. The total economic burden of premature death and disability from cancer reached \$895 billion in 2008, excluding direct medical costs, representing 1.5% of world's gross domestic product (GDP) [15].

Lung, bronchus, and trachea cancers have the largest economic cost on the global economy (about \$188 billion), and it is mostly related to tobacco smoking, which justifies the international efforts for tobacco use control. Colorectal and breast cancers are the 2nd and 3rd largest costs (about \$99 billion and \$88 billion, respectively). In developing countries, cancers of the mouth, cervix, and breast have the greatest impact [16].

Since cancer is expected to become the leading cause of death worldwide, targeted prevention and treatment strategies can save lives and improve the prospects of economic development in many nations. Cancer survivorship is projected to increase because of the improvement in diagnosis due to advances in screening, detection, and treatment [17–19].

## 1.5 Cancer Etiology

The demographic transition is the key driver of the unprecedented growth in cancer burden. Economic development allows the increasing population growth, ageing, and the adoption of lifestyles and behavioral exposures commonly observed in industrialized countries, which account for at least 35% of the cancers [20].

Tobacco smoking is the most important acquired risk factor. Alcohol intake, ultraviolet exposure, and ionizing radiation exposure are associated with the incidence of particular types of cancer. Eating habits also influence cancer development markedly; energy-rich and a highly processed food intake contribute to a low fruit and vegetable diet, which is associated with a lack of physical activity, being overweight, and obesity. Chronic infections play a major role in common cancers in parts of Africa and Asia, and become less important in Europe and North America [6, 21].

### ***1.5.1 Tobacco Use***

Numerous studies have shown an indubitable causal association between tobacco use and at least 14 different types of cancer, including sites that directly receive the tobacco (e.g., the oropharynx and lungs) and other sites that are reached by circulating components (e.g., the pancreas and urinary bladder). Tobacco smoke contains >7,000 chemical compounds, many of which are known carcinogens (e.g., polycyclic aromatic hydrocarbons, N-nitrosamines, and aromatic amines), causing harm via multiple pathways, including deoxyribonucleic acid (DNA) binding and mutations, inflammation, oxidative stress, and epigenetic changes. The risk of smoking related cancer is influenced by the number of cigarettes smoked, duration of the habit, and composition of the tobacco used [6].

In many low-income countries, there is a significant increase in the prevalence of female smokers, while in some developed countries, effective control measures have further discouraged tobacco use in both sexes [6, 22].

### ***1.5.2 Alcohol Consumption***

Some meta-analyses established that a significant positive dose-response association exists between alcohol use and cancers of the mouth, pharynx, esophagus, colorectum, liver, larynx, and breast. According to the dose consumed, the risk of mortality seems to be exponential for the upper digestive tract (except mouth and oral cavity) and breast cancers. Survey findings indicate an important synergistic relationship between tobacco and alcohol use, which raises the risk of cancer of the oral cavity, pharynx, larynx, and esophagus [23].

Alcoholic beverages contain several carcinogenic compounds (e.g. ethanol, ethanol acetaldehyde, aflatoxins, ethyl carbamate), which probably affect different pathways. The mechanisms involved are partly understood and possibly include a genotoxic effect of acetaldehyde, the induction of cytochrome P450 2E1 and associated oxidative stress, an increased estrogen concentration, and changes in folate metabolism and in DNA repair. The consumer genotype influences the effects of alcohol consumption and the risk of digestive tract cancers. A deficiency in

aldehyde dehydrogenase 2 (ALDH2) secondary to the ALDH2 Lys487 allele increases the risk of esophageal cancer for the same amount of alcohol consumed [24].

### ***1.5.3 Diet Habit, Obesity, and a Sedentary Lifestyle***

Although there is an inferred association with breast, colorectal, and prostate cancers in developed countries, fat intake has consistently shown a little relationship with their increased risk. According to several trials and a meta-analysis, a high intake of red processed meat was correlated with a greater risk of CRC [25]. The previous hypothesis associating low cancer risk to high intake of fruits and vegetables has not been supported by prospective studies [6]. Similarly, the supposed relationship between a high fiber intake and the decrease in the CRC incidence has not been confirmed by prospective surveys; however, an inverse relationship was observed in the European Prospective Investigation into Cancer and Nutrition study. A higher consumption of milk or dairy products, an increased serum vitamin D level, and folate intake was associated with a lower risk of CRC, and this was supported by the confirmed relationship between a genetic polymorphism in methylenetetrahydrofolate reductase, an enzyme involved in the folate metabolism, and the risk of CRC [6].

According to the cancer site, obesity seems to increase the incidence and mortality risks through different mechanisms, in a linear fashion with a higher body mass index. The higher prevalence of gastroesophageal reflux among obese individuals is probably associated with an increased risk for esophageal adenocarcinoma. The higher circulating estradiol in postmenopausal women, formed in adipose tissue, increases the risk of breast and endometrial cancers. For cancers of colon in men, pancreas, kidney, gall bladder in women, malignant melanoma, ovary, thyroid, non-Hodgkin's lymphoma, multiple myeloma, and leukemia, the mechanisms involved are less clear [6].

### ***1.5.4 Infections***

There is strong evidence that relates chronic infections by biological agents as risk factors for specific cancers. The population attributable fraction for oncogenic agents of the 12.7 million new cancer cases in 2008 was 16%, mainly due to *Helicobacter pylori*, the hepatitis B and C viruses (HBV and HCV), and the human papillomaviruses (HPV), which is higher in developing countries (26%) than in developed countries (8%). In women, cervix cancer accounted for about half of the infection-related burden of cancer; in men, liver and gastric cancers accounted for >80% [6, 26].

The causal association between chronic infection with *Helicobacter pylori* and the risk for non-cardia gastric adenocarcinoma, mucosa-associated lymphoid tissue, and diffuse large B-cell lymphoma is well established. Chronic infection with HBV is one of the most important causes of hepatocellular carcinoma (HCC) worldwide, particularly in highly endemic areas in Asia and Africa. HPV infection causes pre-cancer and cancer (mainly squamous cell carcinoma) of the cervix, anus, vulva, vagina, penis, and oropharynx.

Once the human immunodeficiency virus (HIV)-advanced infection causes immunosuppression, HIV-positive individuals have an increased cancer risk, as observed in the acquired immunodeficiency syndrome-defining cancers, Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer. HIV typically coexists with oncogenic viruses, notably the Epstein-Barr virus, HPV, HBV, and HCV, and this raises the risk of lymphoma, anogenital, and liver cancer, respectively [6].

## 1.6 Cancer Control

### 1.6.1 Screening

#### 1.6.1.1 Lung Cancer Screening

Recently, the National Lung Screening Trial (NLST) used three annual low-dose computed tomography (LDCT) scans on individuals aged 55–74 years with a 30-pack/year history of cigarette smoking or former smokers that quit within the previous 15 years. Compared to the chest radiography screening, LDCT provided a 20% reduction in the lung cancer mortality over a median of 6.5 years of follow-up [27].

Consequently, the United States Preventive Services Task Force (USPSTF) recommended annual screening for adults aged 55–80 years with a similar profile as previously described [28]. Nevertheless, prior to implementing widespread screening, the potential risks must be weighed, including the applicability of the controlled trial conditions in actual practice, complications associated with the management of a great number of false-positive results in the NLST (96.4%), the potential harmful effects of the overdiagnosis of indolent cancers, the cost effectiveness, and radiation exposure [29].

#### 1.6.1.2 Breast Cancer Screening

In many high- and middle-income countries, population-based screening programs have been established for decades, achieving significant reductions in related mortality. Evidences indicate showed a 20% reduction in breast cancer mortality in the screening group versus the control [30].

Mammography screening is the only effective screening method, with an increase in the replacement of the screen-film technique by digital mammography. It is strongly recommended in women aged 50–69 years, typically at 2-year intervals. Biennial screening at age 40 years and after 69 years yielded some additional mortality, although it consumed more resources and increased overdiagnosis and overtreatment [30].

Although there is no evidence of benefit for breast self-examination, this practice appears to improve breast awareness. Clinical breast examination seems to reduce the diagnoses of advanced-stage breast cancer [30].

### 1.6.1.3 Colorectal Cancer Screening

The benefits of CRC screening have been shown with accumulating evidence over the last two decades. Since its validation, population-based screening programs have been introduced in developed countries, reducing the incidence, mortality, and burden of the disease, yet they remain absent in most of the developing countries [31].

The premise of CRC screening is grounded in the role of fecal occult blood testing (FOBT), flexible sigmoidoscopy or colonoscopy in the early detection of pre-cancerous polyps, which prevents progression to CRC considering the adenoma-carcinoma sequence, making CRC screening highly suited for preventive care.

The screening is generally offered to individuals aged 50 years, since >90% of all CRC occur after this age, and screening is extend to 74 years. Most of the screening protocols include the isolated or combined approach of annual or biennial FOBTs and endoscopic techniques with recommended intervals varying between 2 years and 10 years, according to the findings [32].

Colonoscopy remains the most effective method, because it allows direct visualization and removal of the lesions in single procedure. In contrast, poor compliance is a major barrier due to the uncomfortable bowel preparation, directing efforts to the development of more acceptable, practical, and less invasive tests with a high sensibility. New screening methods such as virtual colonoscopy and multiple target DNA testing in stool samples are available, but these are still under improvement and further investigations [33].

### 1.6.1.4 Prostate Cancer Screening

It was believed that the screening of asymptomatic men for the early detection of prostate cancer with prostate-specific antigen (PSA) and digital rectal exam was the best strategy for reducing mortality, however, the present evidence is not sufficiently conclusive to establish its role.

Two large international studies that tested prostate cancer screening for mortality after a 13-year follow-up reported different results [34, 35]. The European Study

of Screening for Prostate Cancer noted a 21% mortality reduction in the PSA-based screening group versus the control. Conversely, the Prostate, Lung, Colorectal, and Ovary trial indicated that there was no benefit in mortality reduction in the annual screening group versus the control. As a result, the USPSTF published a review of its previous recommendations contrary to this routine performance [28].

Arguments against PSA-based screening include the overdiagnosis of indolent disease, overtreatment, and complications caused by biopsies and treatment (e.g., urinary incontinence and erectile dysfunction). Most of the international screening programs for prostate cancer currently support informed decision-making and a risk-based approach.

### 1.6.1.5 Cervical Cancer Screening

The impact of population-based cervical cancer screening programs is evident by the strong downward trend in the incidence and effective decrease in cancer-specific mortality by 50–80% in the highest-income countries [36].

Cervical cancer screening is generally offered to women from the ages of 25–30 years to 60–65 years. The recommended interval commonly varies between 3 and 5 years, depending on the previous result and the screening method used. Screening tests include cervical sampling for conventional or liquid-based cytology, molecular testing for HPV infection, and visual inspection of the cervix with acetic acid. Recently, cervical cancer screening by HPV testing has been established as the most accurate and effective method [37].

Among women living with HIV, the cervical cancer screening should be initiated as soon as they test positive for HIV, regardless of age, because of the higher risk of persistent HPV infection and the premature development of precancerous and cancerous lesions.

## 1.6.2 Chemoprevention

Over the past decades, great efforts have been made in cancer chemoprevention strategies through the administration of synthetic, natural, or biological drugs and other compounds to inhibit, delay, or reverse the carcinogenic process with a potential impact on cancer-related incidence and mortality [38, 39].

The Breast Cancer Prevention Trial demonstrated a reduction of 50% in breast cancer in higher risk women using tamoxifen for 5 years versus placebo, however, it was observed an increased risk of endometrial carcinoma and thromboembolic events, confirmed by the International Breast Cancer Intervention Study-1 [40]. The Study of Tamoxifen and Raloxifene trial showed that raloxifene was less effective in reducing invasive breast cancer, but it had a safer profile than tamoxifen [41]. Recent analyses indicated that other aromatase inhibitors (e.g., anastrozole) also have a chemopreventive effect, especially in postmenopausal women [42].

Previous trials that primarily have shown reductions in the CRC development and mortality with the use of nonsteroidal anti-inflammatory drugs [43]. Daily aspirin reduced the CRC risk by 24% and the related mortality by 21–35% [44]. Selective cyclooxygenase 2 inhibitors reduced adenoma development in familial adenomatous polyposis by 28%; nevertheless, they were associated with an increased risk of cardiovascular events [38].

Regarding prostate cancer chemoprevention, two large trials compared 5 $\alpha$ -reductase inhibitors (i.e., dutasteride and finasteride) versus a placebo and showed a reduction in cancer diagnosis, especially for lower grade tumors [45, 46].

Among the trials with negative and harmful results, two attempted to link lung cancer risk reduction to carotenoids intake. Both showed increased new cases and deaths from lung cancer and cardiovascular disease, particularly in current or former smokers in the  $\beta$ -carotene group [38, 39].

### 1.6.3 Vaccines

In the 1980s, after a mass vaccination of children and teenagers in Taiwan, the rates of chronic hepatitis B decreased remarkably from 9.8% to <0.7%, leading to a 50% drop in the rates of mortality from HCC in the same population. Therefore, vaccines against HBV constitute a part of the current childhood vaccination programs worldwide, and are expected to reduce the incidence of adult HCC [47, 48].

Currently, highly effective prophylactic bivalent and quadrivalent vaccines are available to prevent infection, especially against oncogenic HPV types 16 and 18, both responsible for 70% of cervical cancer cases. The efficacy and cost-effectiveness are maximal among previously unexposed women; therefore, vaccination is being implemented progressively among adolescent girls in 2- or 3-dose schedules. Immunization is efficacious for preventing infection and lesions at all investigated anatomical sites [49, 50].

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# Chapter 2

## Understanding Cancer Stem Cells Biology to Get Rid of Tumours



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**Abstract** Recent advances in oncology have evidenced the existence of a sub-population of cells, the cancer stem cells (CSC), which self-renew and are able to originate differentiated tumour cells responsible for the overall organization and heterogeneity of the tumour tissue. CSC have been identified and isolated from a wide range of human tumours, including solid tumours, and are thought to play a central role in the tumour initiation, progression and metastatic ability, as well as resistance to conventional cancer treatment and relapse of the tumours. Studies of animal models and human cancers, as well as advances in the understanding of the biological processes regulating normal tissue stem cells have provided further knowledge into CSC biology. Here, we present the specific characteristics of CSC, the functional similarities shared with normal tissue stem cells, including the signaling pathways and microenvironment. We will also address recent advances that have revealed the complexity of these cells and present new prospects in the treatment of cancer by a combined use of standard therapies with agents specifically targeting CSC.

**Keywords** Stem cells · Cancer · Markers · Microenvironment · Therapeutic strategies

### 2.1 Introduction

Stem cells are defined by a high proliferative potential, the ability to generate cells with similar properties upon division (self-renewal) or to give rise to cells differentiated into one or multiple cell types (potency). Stem cells division might occur in three modalities: i) a symmetric renewal of the stem cell by division into two identical daughter cells; ii) a symmetric commitment of the stem cell by division into two

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differentiated daughter cells; and iii) an asymmetric division generating a stem cell and a differentiated cell.

Embryonic stem cells (ESC) have an unlimited proliferation capacity, and are pluripotent cells since they preserved the potential to differentiate into all cell types of the adult organism [1–3]. Adult tissues and organs of higher vertebrates are mostly constituted of fully differentiated and specialized cells forming the tri-dimensional layout and enabling the biological functions of those tissues/organs, and a rare population of specific stem cells with restricted ability to differentiate into the mature cell types constituting the tissues/organs where they reside [4]. Adult stem cells (ASC) have been studied extensively and characterized in tissues and organs with fast turnovers, such as hematopoietic, intestinal and skin stem cells [4], and identified also in organs considered “post-mitotic” such as the brain or the heart [5, 6]. Adult tissues/organs are organized hierarchically with ASC at the apex, and then fully differentiated cells and cells at various intermediate stages of differentiation, also frequently called progenitors. This organization provides cellular heterogeneity within the tissues. Interestingly, ASC are located in defined microenvironments, called niches which provide molecular cues for ASC to either remain quiescent, proliferate or differentiate when necessary [7].

The concept stating that tumours might originate from a population of cells with stem cells properties was disregarded in favour of a prevailing genetic model predicting that cancer initiation and progression resulted from the cumulative acquisition of genetic alterations by normal somatic cells [8, 9]. In this model, the transformed tumour cell loses its specialized cell-type attributes and progressively dedifferentiates acquiring enhanced proliferation and reduced capacity to undergo apoptosis. Tumours would then be comprised of cells with indefinite proliferation capacities and each viable cancer cell of the tumour would have the same potential to grow a new tumour. However, this latter fact has been proven to be incorrect, and only few cells within the tumour can propagate tumours into immune-compromised mouse models [9]. The cancer stem cell (CSC) concept states that most of the cells within a tumour are originated from a small subset of multipotent CSC able to self-renew with unlimited proliferative ability, capable of initiating and maintaining the heterogeneity of tumour cells by asymmetrical cell division and differentiation into non-tumorigenic cells which form the bulk of the tumour [9].

## 2.2 Specific Characteristics of CSC and Normal Tissue Stem Cells

In mammals, all cells of the embryo and the adult organism originate from the fertilized oocyte, characterized by the capability to give rise to extra-embryonic structures, such as the foetal portion of the placenta, umbilical cord and extra-embryonic membranes [10]. Collectively, these features define the oocytes and their early progeny cells (blastomeres – cells from morula at the stage 2–8 cells) as totipotent [10].

Additional cell divisions lead totipotent cells to form the blastocyst, an embryonic structure which comprises an outer cell layer (trophoblasts) forming an inner cavity with an aggregate of embryonic cells at one pole, named the inner cell mass (ICM). Trophoblast cells originate the extra-embryonic tissues, while cells of the ICM generate the epiblast, and are precursors of the three germ layers from which all cells of the future embryo are derived. ESC isolated from the ICM have an unlimited self-renewal and proliferation capacity in culture and are pluripotent cells, since they preserved the potential to differentiate into all cell types of the adult organism [1–3, 11, 12]. In mouse, unlike ESC which were isolated from blastocysts prior to implantation, stem cells isolated from mouse blastocysts immediately after implantation in the uterus, named epiblastic stem cells (EpiSC), are inefficient for the colonization of the host blastocyst [13, 14]. Interestingly, mouse EpiSC and human ESC which retain the capacity to differentiate into cell types of the three germ layers indicating their pluripotent nature, share similar gene expression profiles, differentiation potentials and culture conditions for self-renewal. Most of the tissues/organs of higher vertebrates also have a minute population of specific multipotent ASC with a differentiation potential restricted to the cell lineage repertoire of the organs/tissues where they are resident [15], and only occasionally divide to contribute to the organ homeostasis and functions over lifetime [7].

CSC were originally described in acute myeloid leukaemia, and displayed surface markers distinct from those of other less proliferative tumour cells [16]. It was proposed that malignant leukaemia stem cells resistant to chemotherapy and radiation therapy, capable of recapitulating the acute myeloid leukaemia when transplanted into immuno-deficient mice, resulted from the transformation of non-pathological hematopoietic stem cells and were present in small amounts in patients. As a result, a general model based on CSC has been proposed for other tumour types [8]. Like ASC, CSC are present in small numbers within the tumour, self-renew, have unlimited proliferative ability and originate non-tumorigenic cells forming the bulk of the tumour [17, 18]. CSC have now been characterized in solid tumours, such as glioblastoma, breast, lung, ovarian, prostate, skin and gastric epithelial cancers [16, 19–23]. The genetic model stating the establishment of cancer by cumulative acquisition of genetic alterations and the CSC concept might in fact be complementary rather mutually exclusive [9, 24]. Indeed, CSC may derive from normal tissues stem cells or progenitors that have gained oncogenic mutations and lost their ability to self-regulate proliferation, and/or through genetic and epigenetic defects that instate a self-renewal capacity in even more mature cells [8, 25, 26]. Oncogenic changes are often the result of inherited mutations or induced by environmental cues such as UV light, X-rays, chemicals, tobacco products, and viruses [27]. Altogether, genetic and epigenetic modifications, as well as interactions between CSC and the microenvironment confer the heterogeneity of the tumours which directly impacts on the patient survival [28].

CSC share similarities with normal stem cells, turning difficult the implementation of efficient treatments targeting and neutralizing specifically CSC. A need to specifically detect CSC amongst other cells has led to the identification of marker molecules for liquid and solid tumours such as surface adhesion molecules and cytoprotective enzymes (Table 2.1), and occasionally revealed the expression of

**Table 2.1** Examples of normal and cancer tissues and stem cell markers

Marker	Description	Expression in normal tissues or stem cells	Expression in tumours or cancer stem cells
ALDH1	NAD(P) <sup>+</sup> -dependent enzyme oxidizing retinaldehyde to retinoic acid and acetaldehyde to acetic acid	Breast adult	Medulloblastoma, glioma, head and neck cancers, lung, breast, pancreas, bladder, prostate
BMI-1	Component of multiprotein transcriptional repressor Polycomb group PRC1-like	Hematopoietic, neural, intestine, breast and prostate	Breast, prostate, neuroblastomas, leukemias
CD29/Integrin- $\beta$ 1	Membrane protein involved in cell-cell and cell-extracellular matrix adhesion, essential for cell proliferation, migration, invasion and survival	Hematopoietic and mesenchymal stem cells, and hematopoietic and endothelial progenitors	Breast, colon
CD24/heat stable antigen	Glycoprotein marking exosomes, binding to P-Selectin on activated platelets and vascular endothelial cells	B and T immune cells, keratinocytes, myofibres and neuroblast	Breast, pancreas, liver, oesophagus, gastric
CD34	Transmembrane adhesion protein	Hematopoietic and mesenchymal stem cells, hematopoietic and endothelial progenitors	Leukemias, sarcomas
CD44	Membrane adhesion protein and hyaluronan receptor, important for cell proliferation, differentiation, migration, angiogenesis, presentation of cytokines, chemokines, and growth factors to their receptors, and docking of proteases at the membrane	Hematopoietic stem cells and progenitors, pluripotent stem cell	Breast, pancreas, liver, oesophagus, gastric
CD90/Thy-1	Glycoprotein involved in cell-cell and cell-matrix interactions anchored to membrane by glycosylphosphatidylinositol-expressed mainly in leukocytes	Thymus and hepatic progenitors, mesenchymal and hepatic stem cells	Breast cancer, glioblastomas
CD105/Endoglin	Integral transmembrane glycoprotein, TGF $\beta$ R2 co-receptor for TGF- $\beta$ and mediating fetal vascular/endothelial development	Vascular endothelial cells, chondrocytes, syncytiotrophoblasts of term placenta and mesenchymal stem cells	Osteosarcomas, leukemia, ovarian, laryngeal and gastrointestinal stromal cancers, melanoma

CD117/c-kit	Membrane-bound or soluble growth factor, also called Stem Cell Factor (SCF) expressed by fibroblasts and endothelial cells promoting proliferation, migration, survival, and differentiation of hematopoietic progenitors, melanocytes, and germ cells.	Progenitor cells	Breast, ovarian, lung, glioblastomas
CD133/ Prominin-1	Transmembrane glycoprotein expressed in membrane protrusions and binding cholesterol	Hematopoietic and glial stem cells, kidney, mammary gland, salivary glands, testes and placental cells and endothelial progenitor cells	Prostate, gastric, and breast carcinomas, glioblastomas, melanomas
CDw338/ ABCG2	Efflux protein involved in detoxification of xenobiotic substrates in various organs such as liver, intestine, placenta, and blood brain barrier	Embryonic and hemopoietic stem cells, various adult stem cells	Glioma/Medulloblastoma, head and neck cancers, lung, prostate, melanoma, osteosarcoma
NANOG	Transcription factor part of the core pluripotent factors acting closely with OCT4 and SOX2, involved in the maintenance of pluripotency and self-renewal of embryonic stem cells	Embryonic stem cells and induced pluripotent stem cells (iPSC)	Breast, cervix, oral, kidney, prostate, lung, gastric, brain, and ovarian cancer, lung adenocarcinoma cells
NESTIN	Class VI intermediate present in vertebrates, marker of Neural stem cells both during development and adult brain.	Neural stem cells, brain progenitor and hematopoietic progenitors	Glioblastomas, melanomas
OCT4	Transcription factor part of the core pluripotent factors acting closely with NANOG and SOX2, involved in the maintenance of pluripotency and self-renewal of embryonic stem cells	Embryonic stem cells and induced pluripotent stem cells (iPSC)	Many carcinomas, ovarian, endometrium and lung adenocarcinoma
SCA-1	Glycosyl phosphatidylinositol-anchored cell surface protein	Stem cells, such as hematopoietic stem cells and progenitors, and differentiated cells in a wide variety of tissues/organs	Breast and prostate

(continued)



Table 2.1 (continued)

Marker	Description	Expression in normal tissues or stem cells	Expression in tumours or cancer stem cells
SOX2	Activator or suppressor of transcription acting closely with OCT4 and NANOG, involved in the maintenance of pluripotency and self-renewal of embryonic stem cells	Embryonic stem cells, induced pluripotent stem cells (iPSC) and neural stem cells	Glioblastomas, medulloblastoma, oligodendroglioma, melanoma, osteosarcoma, prostate, small-cell lung cancer, lung squamous cell carcinoma, lung adenocarcinoma, non-small cell lung cancer
<b>H type 1</b>	Stage-specific embryonic antigen-5 (SSEA-5), carbohydrate-associated molecule involved in controlling cell surface interactions during development, carried on proteins Fuc $\alpha$ 1-2Gal $\beta$ 1-3GlcNAc $\beta$ 1-	Embryonic stem cells and induced pluripotent stem cells (iPSC)	Germ cell carcinomas
<b>CD15</b>	Lewis X, stage-specific embryonic antigen-1 (SSEA-1) carbohydrate-associated molecule involved in the control of cell interactions during development carried on lipids or proteins Gal $\beta$ 1-4[Fuc $\alpha$ 1-3]GlcNAc $\beta$ 1-3Gal $\beta$ 1-	Embryonic, mesenchymal and neural stem cells	Glioblastomas
<b>CD60a/GD3</b>	Ganglioside, messenger in apoptosis induced by CD95 pathway NeuAc $\alpha$ 2-8NeuAc $\alpha$ 2-3Gal $\beta$ 1-4Glc $\beta$ 1-	Neural stem cells	Differentiated germ cell carcinomas, melanomas
<b>CD77/Gb3</b>	Globotriaosylceramide antigen, Burkitt lymphoma antigen Gal $\alpha$ 1-4Gal $\beta$ 1-4Glc $\beta$ 1-	Activated B-cells located in tonsil, mucosal lymphoid tissues, peripheral blood, bone marrow and spleen.	Burkitt lymphoma, breast cancer, germ cell carcinomas
<b>CD173/H type 2</b>	Saccharide antigen carried on proteins or lipids, expressed mainly during early hematopoiesis, on endothelial and bone marrow stromal cells Fuc $\alpha$ 1-2Gal $\beta$ 1-4GlcNAc $\beta$ 1-	Embryonic, mesenchymal and neural, hematopoietic progenitors	
<b>CD174</b>	Lewis Y, carried on proteins or lipids on erythrocytes Fuc $\alpha$ 1-2Gal $\beta$ 1-4[Fuc $\alpha$ 1-3]GlcNAc $\beta$ 1-	Hematopoietic progenitor cell	Breast cancer
<b>CD175</b>	Histo-blood group carbohydrate structures carried on proteins GalNAc $\alpha$ 1-	Embryonic stem cells	

<b>CD176</b>	Thomsen-Friedenreich antigen, core-1; expressed on glycoproteins and glycosphingolipids Galβ1-3GalNAcα1-	Embryonic stem cells	Diverse carcinomas and leukemias
<b>GD2</b>	Glycosphingolipids containing the sialic acid residues in their carbohydrate structure GalNAcβ1-4[NeuAcα2-8NeuAcα2-3]Galβ1-4Glcβ1-	Neural and mesenchymal stem cells	Differentiated germ cell carcinomas, breast cancer, melanomas
<b>Gb4</b>	Globoside characterized as a stage-specific embryonic antigen (SSEA), highly expressed during embryogenesis GalNAcβ1-3Galα1-4Galβ1-4Glcβ1-	Germ cell carcinomas	Germ cell carcinomas
<b>Gb5</b>	Globoside stage-specific embryonic antigen-3 (SSEA-3), highly expressed throughout preimplantation in mouse Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glcβ1-	Embryonic stem cells, induced pluripotent (iPSC) and mesenchymal stem cells	Breast cancer, germ cell carcinomas
<b>Sialyl-Gb5</b>	Stage-specific embryonic antigen (SSEA-4), highly expressed throughout preimplantation in mouse NeuAcα2-3Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glcβ1-	Embryonic stem cells, induced pluripotent (iPSC) and mesenchymal stem cells and breast progenitor cell	Germ cell carcinomas
<b>Globo-H</b>	Antigenic carbohydrate carried on proteins or lipids Fucα1-2Galβ1-3GalNAcβ1-3Galα1-4Gal-		Various types of cancers, often in cancers of breast, prostate and lung at the cell surface
<b>TRA-1-60</b>	Tumor-recognition antigen; carried on protein Sialylated keratan sulfate proteoglycan	Embryonic and mesenchymal stem cells	Teratocarcinomas

Adapted from elsewhere [27, 31, 35, 36]. Markers in bold and Italics indicate carbohydrate stem cell markers

master regulators of pluripotency, such as OCT4, SOX2 and NANOG, normally repressed in somatic cells, suggesting that these factors may assist in the pathological process of conversion of non-tumorigenic cells into CSC [27, 29, 30]. CSC may also express drug-efflux transporters and pumps (such as ATP-binding cassette (ABC) drug transporters, and multidrug resistance transporter 1). Most of these markers are present in non-tumorigenic cells and even in normal stem cells, and do not clearly distinguish CSC from other cells. Researchers are now exploring novel CSC non-protein markers and found that the composition of glycans is altered during the malignant conversion process, generating tumour-specific glycans that might be used as specific cell-surface CSC markers [31]. Finally, some microRNA are enriched in tumours, such as in lung, prostate and colorectal cancer and function as oncogenes, while other microRNA such as Let7 are frequently down-regulated in tumours such as breast and lung cancer and function as a tumour suppressors [32–34].

### 2.3 Signalling Pathways and Microenvironment

Niches are complex structures integrating interactions between stem cells and the neighbouring cells (such as stromal, mesenchymal and immune cells) either by direct interactions or by secretion of signalling factors [37, 38]. Both stromal and stem cells also interact with the extracellular matrix, a complex network of macromolecules. The disorganization of the interactions existing within the niche might provide strong signals for normal stem cells to proliferate and/or differentiate, and may favour tumour initiation and progression, in combination with other stimulations such as inflammation and angiogenesis [39]. Like normal stem cells, CSC depend on the microenvironment cues to retain their ability to self-renew or differentiate [38], and the niche contributes to their resistance to therapy by sheltering them from the genotoxic treatments [40, 41]. Aberrant activation of key signalling pathways and/or their mediators (such as Hedgehog, Notch, Wnt/ $\beta$ -catenin, HMGA2, Bcl2, Bmi-1) involved in the control of self-renewal, proliferation and differentiation of normal stem cells may also contribute in the acquisition of new stemness properties by CSC [42]. Moreover, the microenvironment of many ASC is hypoxic (low oxygen tension) and modulates their self-renewal, proliferation and cell-lineage commitment [34, 43]. A Notch and hypoxia-induced pathway synergistic effect is correlated with increased metastatic tumour potential and poor survival of patients, suggesting that a crosstalk between these pathways is essential to cancer initiation and progression [43].

## 2.4 New Prospects in Treatment

Standard cancer treatments by chemotherapy, radiotherapy and surgical ablation have mostly focused on shrinking the tumour size, but CSC might persist after therapy and cause the tumour to relapse. Indeed, CSC may escape treatment due to different sensitivities and specificities to the radiation or chemotherapy used, but also because they have already metastasized in patients newly diagnosed with cancer [44]. In some patients, CSC are in a dormant state, and stress or inflammation reactivate their proliferation and differentiation by release of pro-inflammatory cytokines and chemokines, such IL-6, IL-8, MCP1, CCL5 [45, 46]. Even more worrying, the conventional radiation and chemotherapy may increase CSC numbers in a process analogous to the normal repair-process during tissue damage, by which dying cancer cells might release cytokines that stimulate CSC proliferation and/or differentiation [47, 48]. Thus, to implement efficient treatments targeting specifically CSC and preventing tumour recurrence, new approaches are being developed to destabilize CSC stemness [48]. One strategy is to inhibit the signalling pathways promoting self-renewal and survival of CSC, such as Hedgehog, Notch, Wnt/ $\beta$ -catenin using combinations of specific inhibitors affecting these pathways. A limitation to this approach is the necessity of these pathways for normal stem cells function in patients. Nevertheless, preclinical and clinical studies with Notch signalling inhibitors showed the decrease in the number of breast CSC in animal models, and a promising decline of the disease progression when used in combination with the anti-mitotic compound docetaxel [49]. Moreover, it was recently reported that down-regulation or inhibition by small molecule compounds of BMI-1, a polycomb repressor involved in the maintenance of normal several tissues stem cells or CSC [50–54], diminished CSC proliferation, tumour growth, tumorigenic potential and limited metastasis [55, 56]. CSC may also be resistant to conventional chemotherapy due to overexpression of detoxifying enzymes, membrane transporters or pumps enhancing the elimination of pharmacological agents [57]. Several groups have reported an increase of sensitivity to chemotherapy and radiation by treatment with drugs targeting these transporters *in vitro* and *in vivo* in lung cancer cells [58]. The inhibition of aldehyde dehydrogenase activity, a hallmark of human breast carcinoma CSC [59], by inhibitors such as diethylamino-benzaldehyde or all-trans retinoic acid led to a decrease of tumour aggressiveness and increased sensitivity to chemotherapy [60].

Targeting CSC specific surface markers or using these markers to enhance CSC death is also a promising strategy. The blockade of overexpressed CXCR1, a IL-8 receptor, in human breast CSC by specific antibodies or by repertaxin, a small inhibitor of CXCR1, reduced tumour growth, CSC numbers and their metastatic potential in animal models [48]. In human melanoma CSC, down-regulation of the CD133 surface marker by RNA interference reduced their metastatic potential in animal models [61]. The recognition of CD133 by specific monoclonal antibodies also led to a specific cytotoxic effect on melanoma CSC and hepatoma cells [61,

62]. The modulation of miRNA expression in CSC might also provide new means to control CSC fate [63]. Indeed, overexpression of miR-34a in prostate CD44-positive CSC, where it is normally down-regulated, inhibited self-renewal of CSC as well as tumour development [64].

Alternative therapeutic strategies aiming to destabilize the interactions between CSC and their niche, and promoting cell cycle entry of quiescent CSC to enhance their sensitivity to chemotherapy/radiotherapy present a great potential. Hypoxia inducible factors (such as HIF-1 and HIF-2) have often been targeted in cancer therapies because they regulate genes critical for tumour cells survival, metabolic adaptation, angiogenesis and metastasis [65]. Anti-angiogenic agents used in cancer therapy might activate HIF factors as a result of hypoxia-induced stress in tumours and might adversely contribute to therapy resistance [65, 66]. Combinations of anti-angiogenic compounds with HIF-inhibitors are currently tested with promising results, such as converting metastatic cervical carcinomas and pancreatic neuroendocrine tumours of animal models into benign lesions [67, 68]. Another strategy envisaged to sensitize quiescent CSC to chemotherapy, is to stimulate their division by cytokines such as interferon- $\alpha$  and G-CSF, or chemical compounds like arsenic trioxide before chemotherapy [69]. Finally, the stimulation of CSC in a tumour to terminal differentiation, resulting in the exhaustion of the cells that initiate and perpetuate the tumour might also be an approach to be considered in future therapies [70, 71].

## 2.5 Concluding Remarks

Understanding of molecular mechanisms involved in CSC biology, their emergence from normal cells, interconnection with the niches and contribution to the tumour heterogeneity should greatly contribute for development of future strategies to eradicate tumours, and improve patient's survival and life quality by targeting specifically CSC in tumours.

### Multiple Choice Questions

1. Which of the following statements does not apply to stem cells in general:
  - A. Stem cells have a proliferative potential
  - B. **Stem cells are always quiescent**
  - C. Stem cells divide symmetrically to self-renew
  - D. Stem cells have the potential to generate differentiated cells
  - E. Stem cells may divide symmetrically or asymmetrically

**Answer:** The purpose of stem cells is to renew cells in tissues, therefore they have to divide at specific times which are different for every stem cell. Some stems cells may remain quiescent for very long periods of time.

2. Which of the following statements about embryonic stem cells (ESC) is CORRECT:

- A. **ESC have the potential to give rise to all the cells of the adult organism**
- B. ESC are multipotent
- C. ESC are a rare population of specific stem cells with restricted ability to differentiate
- D. ESC do not differentiate into cancer cells
- E. None of the above is correct

**Answer:** Pluripotency, which is a characteristic of ESC, indicates precisely their ability to potentially give rise to all the cells of the adult organism, and they can originate TERATOMAS

3. Which of the following statements about adult stem cells (ASC) is **INCORRECT**:
- A. ASC are multipotent
  - B. ASC have been identified in brain tissue
  - C. ASC have been identified in heart tissue
  - D. ASC are the most undifferentiated cells of the tissue where they reside
  - E. **ASC have been not identified in tissues with a fast cellular turn over**

**Answer:** The purpose of stem cells is to renew cells in tissues, and fast turn over tissues have also stem cells to originate all the cells of the tissue

4. Which of the following statements is **INCORRECT**:
- A. **all cells of a tumour have the same potential to grow a new tumour**
  - B. cancer stem cells (CSC) concept states that most of the cells within a tumour are originated from a subset of multipotent CSC
  - C. cancer stem cells (CSC) concept states that CSC initiate and maintain the heterogeneity of the cells in the tumour
  - D. cancer stem cells (CSC) have unlimited proliferative ability and also originate non-tumorigenic cells forming the bulk of the tumour
  - E. cancer stem cells (CSC) have been characterize in solid tumours

**Answer:** It has been proven that all cells from tumours do not have the capacity to generate tumours.

5. Which of the following statements is **INCORRECT**:
- A. Mouse epiblastic stem cells (EpiSC) are pluripotent
  - B. **Mouse epiblastic stem cells (EpiSC) are multipotent**
  - C. Human embryonic stem cells (ESC) are pluripotent
  - D. Human embryonic stem cells (ESC) and mouse epiblastic stem cells (EpiSC) share similar gene expression
  - E. Human embryonic stem cells (ESC) and mouse epiblastic stem cells (EpiSC) have similar gene expression and similar differentiation potential

**Answer:** Epiblastic stem cells are considered the mouse equivalent to human ESC, which are pluripotent, but defined as primed which means they already express genes that are involved in differentiation programs

6. Which of the following statements is INCORRECT:

- A. cancer stem cells (CSC) share similarities with normal stem cells
- B. cancer stem cells (CSC) may express genes which encode master regulators of pluripotency
- C. **master regulators of pluripotency such as OCT4, SOX2 and NANOG are commonly expressed in somatic cells**
- D. Molecular markers present in non-tumorigenic cells may also be expressed in cancer stem cell (CSC)
- E. Molecular markers present in normal stem cells may also be expressed in cancer stem cell (CSC)

**Answer:** Oct4, Sox2 and Nanog are mostly expressed in pluripotent and silenced in other cell types

7. Which of the following statements is INCORRECT:

- A. the stem cell niches are the microenvironment of stem cells
- B. Niches provide signals to stem cells to control self-renewal
- C. Niches provide signals to stem cells to control proliferation
- D. Niches provide signals to stem cells to control differentiation
- E. **cancer stem cells (CSC) do not have niches**

**Answer:** Cancer stem cells have niches and may also create or invade other stem cells's niches when they undergo metastasis

8. Which of the following statements is INCORRECT:

- A. cancer stem cells (CSC) may persist in the patient after surgical ablation of the tumour
- B. cancer stem cells (CSC) remaining in the patient after surgery may cause tumour to relapse
- C. cancer stem cells (CSC) may exist in a dormant state and reactivate their proliferation and differentiation
- D. **cancer stem cells (CSC) existing in a dormant state are never reactivated**
- E. None of the above are incorrect

**Answer:** Cancer stem cells may exist in a dormant state, but for a tumour to develop or grow they have to divide and differentiate

9. Which of the following statements is CORRECT:

- A. Targeting cancer stem cells (CSC) specific surface receptors by antibodies does not affect tumours
- B. Targeting cancer stem cells (CSC) specific surface makers does not affect their properties
- C. **microRNA usage is a promising tool to eradicate cancer cells**
- D. overexpression of microRNA does not affect cancer stem cells (CSC) viability
- E. All affirmations indicated above are correct

**Answer:** microRNA, microRNA mimetics or anti-microRNA are currently tested in clinical trials and showed encouraging results

10. Which of the following statements is INCORRECT:

- A. **Targeting cancer stem cells (CSC) niches to activate CSC division and proliferation may be useful to eliminate CSC**
- B. Hypoxia induced factors inhibitors are not used for therapy
- C. the stimulation of cancer stem cells (CSC) for division may have a negative impact in their elimination
- D. the destabilization of the interactions between cancer stem cell and their niche may present adverse effects for cancer treatment
- E. All affirmations indicated above are correct

**Answer:** The perturbation of stem cells niches may exacerbate their division, proliferation, their differentiation into less harmful cells, and even their death, and consequently exhaust the pool of cancer stem cells

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# Chapter 3

## Apoptosis



**Richard Hill**

**Abstract** Our DNA is continuously assaulted from a plethora of sides including exogenous environmental sources (for examples ionizing radiation (IR) or exposure to environmental genotoxic compounds) and endogenous sources such as replication fork collapse during regular DNA replication, during normal DNA repair events and immunoglobulin V(D)J gene rearrangement. However the incorrect repair of DNA breaks results in significant genomic instability due to gross chromosomal loss, amplification, or rearrangements that can lead to cancer.

**Keywords** Apoptosis · Cell cycle · Cell death

### 3.1 DNA Damage and Repair: The Role of the Cell Cycle and Apoptosis

Our DNA is continuously assaulted from a plethora of sides including exogenous environmental sources (for examples ionizing radiation (IR) or exposure to environmental genotoxic compounds) and endogenous sources such as replication fork collapse during regular DNA replication, during normal DNA repair events and immunoglobulin V(D)J gene rearrangement. However the incorrect repair of DNA breaks results in significant genomic instability due to gross chromosomal loss, amplification, or rearrangements that can lead to cancer. In healthy cells, these harmful effects are controlled by large, multi-component protein complexes, beginning with the detection of DNA damage and the induction of complex protein signalling cascades that ensure genomic integrity. These signalling cascades promote cell cycle arrest, allowing the cell sufficient time to evaluate and where possible to repair the DNA damage. In the presence of sustained damage or when this damage cannot be repaired, the cell can instigate an apoptotic response (programmed cell death) to ensure that the damaged DNA is not passed to daughter cells, thus

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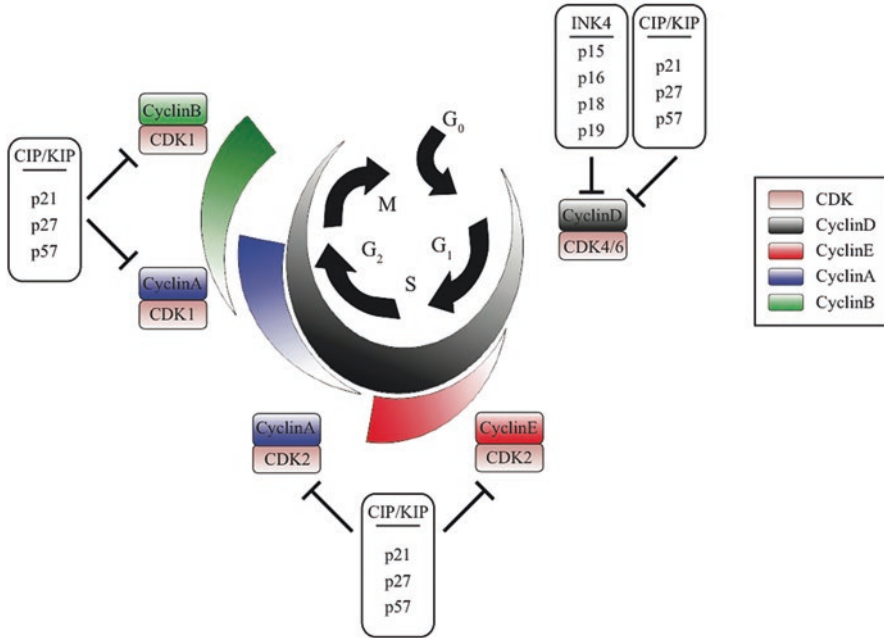
preserving genome integrity. In cancer, these processes are subverted, deregulated and inactivated. Over the course of this chapter the processes, key proteins and pathways involved in the cell cycle, DNA repair and apoptosis will be reviewed with particular focus on disease, in particular cancer and how these components could be therapeutically targeted.

## 3.2 The Cell Cycle

The cell cycle is the process that allows cell division and duplication to occur generating two daughter cells. In eukaryotic cells this cycle can be divided into stages: interphase, where cell growth occurs and the cell accumulates the nutrients required for mitosis preparing it for division and replicating its DNA. There is the mitotic (M) phase, during which the cell splits itself into two daughter cells and the final stage, cytokinesis, where the new cell is completely divided. This can be further divided into specific cell cycle phases, the  $G_0$  phase where the cell has left the cycle and has stopped dividing. The second phase is  $G_1$  (or Gap 1) where the cell increases in size. The  $G_1$  checkpoint control mechanism ensures that everything is ready for DNA synthesis to occur. Once the  $G_1$  checkpoint has been passed, S (synthesis) phase occurs where DNA replication takes place. Following the completion of S-phase, there is the  $G_2$  phase that ensures a temporal gap between DNA synthesis and mitosis allowing continued cellular growth. The  $G_2$  checkpoint ensures that the cell is ready to enter the final M (mitosis) phase of the cell cycle and divide. Cyclin-dependent kinases (Cdks) are serine/threonine-specific kinases that drive cell cycle progression by their interaction(s) with cyclins that mediate the phase transitions within the cell cycle. In contrast to Cdks, the cyclins are an extremely diverse group of proteins classified exclusively by the presence of a cyclin box that binds to Cdk [1]. While most cyclins promote Cdk activity, cyclin-dependent inhibitors (CDKI) restrain Cdk activity. The CDKIs are divided into two classes (that is based on their Cdk specificity and structure). The first class are the Ink4 members (p16<sup>INK4a</sup> [Cdkn2a], p15<sup>INK4b</sup> [Cdkn2c], p18<sup>INK4c</sup> [Cdkn2c] and p19<sup>INK4d</sup> [Cdkn2d]) that predominately target Cdk4 and Cdk6. The second class are the Cip/Kip family members (p21<sup>CIP1</sup> [Cdkn1a], p27<sup>Kip1</sup> [Cdkn1b] and p57<sup>KIP2</sup> [Cdkn1c]) that target cyclin D-, E-, A- and B-dependent kinase complexes. The various phases, proteins, protein-protein interactions and protein abundance throughout the cell cycle are summarized in Fig. 3.1.

## 3.3 DNA Damage and Repair

Our DNA is continuously assaulted by a number of sources, including endogenous sources such as cell metabolism intermediates, replication fork collapse during regular DNA replication and repair events as well as exogenous sources such as the

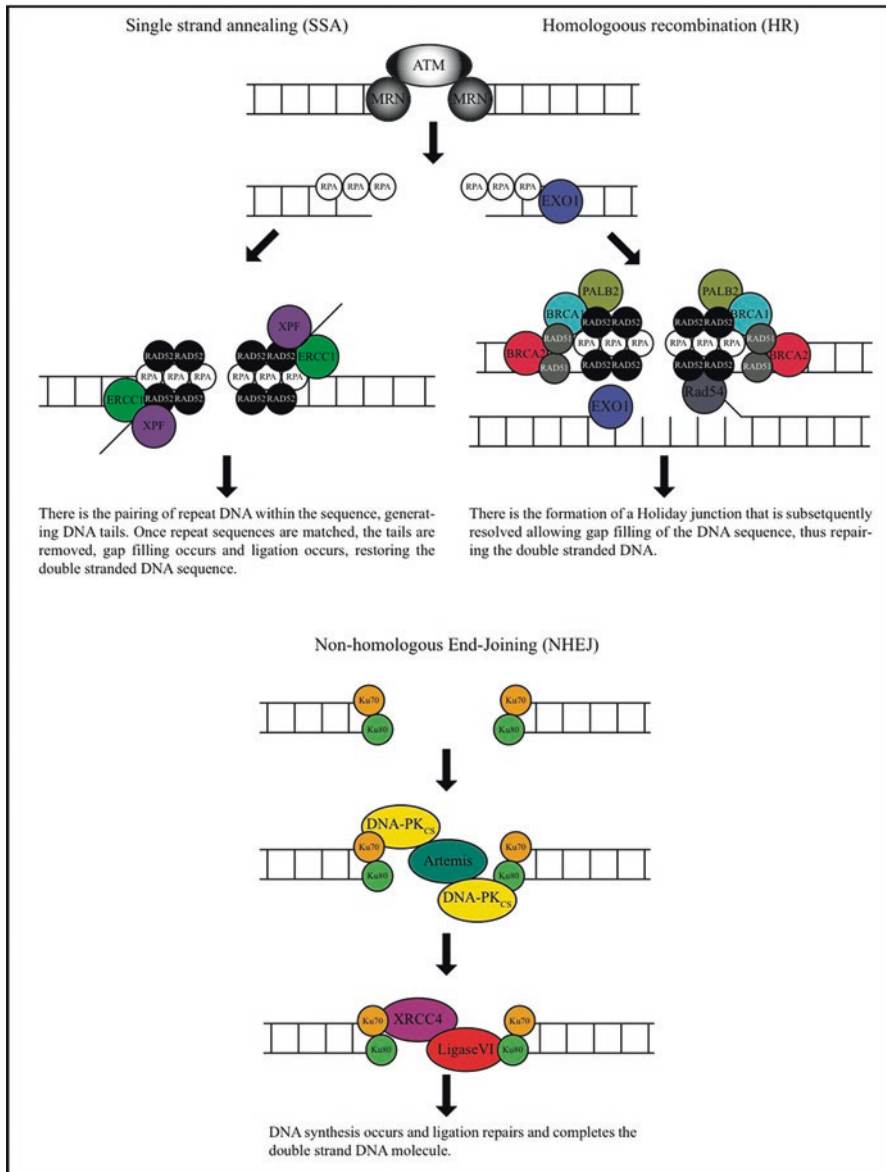


**Fig. 3.1** The cell cycle

environment (for example ionizing radiation (IR) or exposure to genotoxic compounds). In addition the programmed endonucleolytic cleavage of DNA to yield double strand breaks (DSBs) is a natural component of meiotic DNA metabolism and immunoglobulin V(D)J gene rearrangement. DSBs are widely regarded as the most dangerous form of DNA damage, as the incorrect repair of DSBs causes genomic instability in the form of gross chromosomal loss, amplification, or rearrangements that can lead to cancer. In healthy cells, the harmful effects of DNA DSBs are controlled by large, multi-component macromolecular protein complexes, beginning with the detection of DNA damage and inducing complex protein signaling cascades ensuring genomic integrity.

As a consequence of this diverse range of threats, the cell and specifically the cell cycle is armed with DNA damage checkpoints that can stop the cell cycle following DNA damage allowing repair to occur to ensure the faithful transmission of the cells genetic information. These cell cycle checkpoints make certain that the DNA is correctly copied before the instigation of mitosis while the spindle assembly checkpoint inhibits anaphase until all of the chromosomes have been precisely aligned prior to separation. Crucial components of these cellular checkpoints act both directly and indirectly on cell cycle regulators to instigate a cell cycle arrest response as a facet of the DNA damage response (DDR).

Mammalian cells have evolved three mechanisms for the repair of DSBs (summarised in Fig. 3.2): single-strand annealing (SSA), Homologous recombination (HR) and non-homologous end-joining (NHEJ) [2–4]. Single strand annealing



**Fig. 3.2** DNA damage and repair

(SSA) repairs DNA by initially processing the DNA ends to yield overhangs (inevitably leading to large DNA deletions thus is highly error prone) allowing for searching, annealing, and ligation of homologous patches of DNA [5]. The SSA pathway is unique in that it does not require a separate similar or identical molecule of DNA and thus only requires a single DNA duplex, and uses the repeat sequences within

eukaryote DNA as the identical sequence (that are required for homologous recombination) to drive repair. As DNA around the double-strand break site is cut, the single-stranded 3' overhangs that are generated are bound by the RPA protein preventing the 3' overhangs from sticking to themselves. Following RPA binding, the Rad52 protein is recruited to each of the repeat sequences on either side of the DNA break aligning them. This alignment enables the two complementary repeat sequences to anneal. After annealing is complete, leftover non-homologous flaps of the 3' overhangs are cut away by the Rad1/Rad10 nucleases that are directed to the flaps by the Saw1 and Slx4 proteins. At this stage DNA synthesis occurs to complete any remaining gaps and ligation restores the DNA duplex as two continuous strands. The DNA sequence between the repeats is always lost, as is one of the two repeats. Even though there is the significant loss of genetic material during this process, SSA does have a role in DNA repair as the human genome is rich in repeat elements, for example there are over  $10^6$  Alu repeats in the human genome alone [6].

Homologous recombination (HR) is essential to cell division in eukaryotes and in addition to repairing DNA, HR also helps produce genetic diversity when cells divide during meiosis. Whether HR (or NHEJ) is used to repair double-strand breaks is largely determined by the phase of cell cycle. As HR requires an intact sister chromatid it is restricted to the S and G<sub>2</sub> phases of the cell cycle [7]. After a DSB occurs, the MRN protein complex (consisting of Mre11, Rad50 and Nbs1) binds to the DNA on either side of the break after which a resection step occurs cutting back the DNA around the 5' ends of the break. The MRN complex recruits the Ataxia-telangiectasia mutated (ATM) protein as well as the Sae2 protein to mediate signal transduction and generate these short 3' overhangs of single-strand DNA. At this stage the 5' to 3' resection is continued by the Sgs1 helicase and the Exo1 nuclease. Once Sgs1 has opened the dsDNA sequence, the Exo1 nuclease function generates the ssDNA product. At this stage the RPA protein binds the 3' overhangs. The PALB2, BRCA1, BCRA2, Rad51 and Rad54 proteins form a filament of nucleic acid and protein on the single strand of DNA coated with RPA. This nucleoprotein filament then begins searching for DNA sequences similar to that of the 3' overhang. Once the matched sequence is found, the single-stranded nucleoprotein filament moves into (invades) the similar or identical recipient DNA duplex. A displacement loop (D-loop) is formed during this process and once it has occurred, DNA polymerase extends the end of the invading 3' strand by synthesizing new DNA. This generates a Holliday junction. At this stage additional DNA synthesis occurs on the invading strand effectively restoring the strand on the homologous chromosome.

In contrast to SSA and HR, non-homologous end-joining (NHEJ) (which simply pieces together the broken DNA ends) is the predominant repair pathway in mammalian cells [7, 8]. This is because NHEJ does not require a complementary DNA sequence and therefore can be active during any stage of the cell cycle. In NHEJ repair, each broken DNA end is first bound by one Ku70/80 heterodimer, and two heterodimers must come together to bridge matching ends [9] ensuring high fidelity ligation. The resulting complex is subsequently bound by the DNA-dependent protein kinase catalytic subunit (DNA-PK<sub>CS</sub>), phosphorylating target proteins enabling



NHEJ to proceed [10]. *In vitro* studies demonstrated that the Ku heterodimer initially binds to the DNA ends, translocate inwards in an ATP-independent manner and recruits DNA-PK<sub>CS</sub> stabilizing the protein/DNA binding [11–14]. Furthermore, DNA-PK<sub>CS</sub> can join two broken DNA ends together in a complex containing two DNA-PK<sub>CS</sub> molecules acting as a scaffold facilitating the re-joining [15, 16]. The remaining core of the NHEJ apparatus consists of the DNA ligase IV/XRCC4 (X-ray cross complementation group 4 protein) complex [17, 18]. The ligase IV/XRCC4 complex is essential for the ligation stage of NHEJ and is also thought to be involved in the alignment or gap filling of DNA prior to ligation [19]. XRCC4 has been shown to interact with DNA [20], Ku [21], DNA polymerase  $\mu$  [22] and DNA-PK<sub>CS</sub> [18]. In addition to interacting with XRCC4, DNA-PK<sub>CS</sub> phosphorylates XRCC4 *in vitro* and *in vivo* [23, 24]. DNA ligase IV is an ATP-dependent DNA ligase with an amino-terminal catalytic domain that upon complex formation with XRCC4 stimulates its ligase activity [25].

However, these situations becomes significantly more complicated when one considers that regardless of source, DNA damage rarely produces clean breaks allowing straight forward blunt end ligation. Clearly the very nature of DNA damage ensures the cell is faced with a wide range of complex damage preventing efficient ligation presenting the requirement for further processing. The exposed 5' and 3' DNA ends are subject to resection and nucleotide addition/loss thus other components will be required for the NHEJ process to proceed efficiently. For example, the Werner syndrome protein (WRN) can remove 3' phosphate or 3' phosphoglycolate groups generated following IR and is itself phosphorylated by DNA-PK [26]. Interestingly, Artemis is a nuclease with 5' to 3' endonuclease activity that can remove 5' overhangs and shorten 3' overhangs [27] that is phosphorylated by DNA-PK activating the hair pin-opening activity of Artemis [28, 29]. Furthermore Ku80 has been shown to stimulate joining and artemis-mediated processing of DNA ends [30].

While NHEJ is a crucial process to repair DSBs generated by external sources, this process is also absolutely crucial for V(D)J recombination. This process is vital for antibody diversity and normal immune development and is the most widely investigated system for NHEJ (reviewed extensively in [31]). In combination with the RAG1/RAG2 proteins, DSBs are specifically generated. At these break sites, the Ku heterodimer binds to the free DNA ends of the DSB ensuring the spatial arrangement is preserved. DNA-PK<sub>CS</sub> binds the Ku/DNA complex, stimulating DNA-PK activity via phosphorylation enabling the NHEJ reaction to proceed. Furthermore the essential role of DNA-PK in DNA repair and preserving the genome is noted from the phenotype of defective/deleted cells. Cells that lack DNA-PK<sub>CS</sub> are acutely radiosensitive and have defective DSB repair (reviewed in [32]) while mice lacking DNA-PK<sub>CS</sub> remain viable although are immunodeficient (due to the absence of immune development) due to the accumulation of processed but not resolved DNA intermediates [33]. Furthermore DNA-PK<sub>CS</sub><sup>-/-</sup> mice display significant telomeric fusion events consistent with DNA-PK<sub>CS</sub> role in telomere maintenance [34] (discussed below).

Just as it is imperative that our cells can detect and respond to DSBs, it is also crucial that our cells do not recognise the ends of our telomeres as dsDNA breaks. As such DNA-PK has been significantly implicated in telomere maintenance

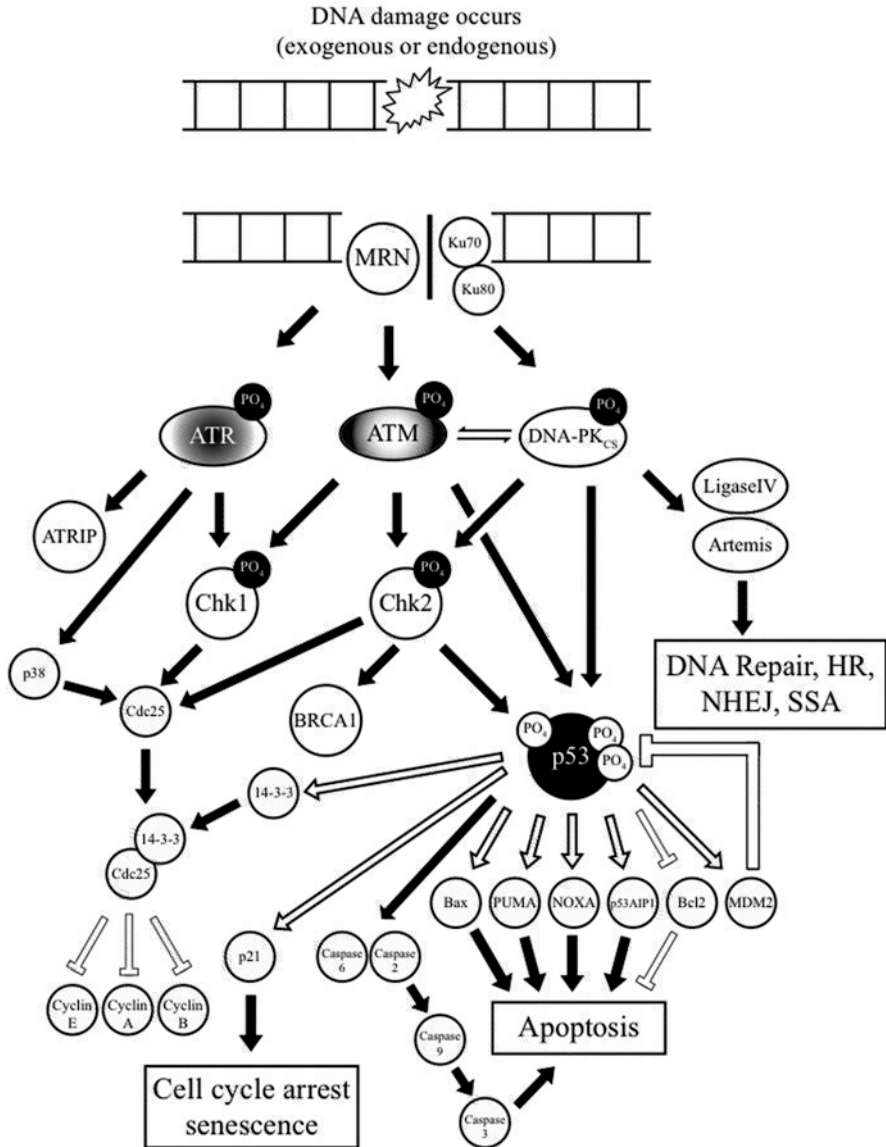
[35–38]. Mouse embryo fibroblasts obtained from DNA-PK<sub>CS</sub><sup>-/-</sup> mice showed significant end-to-end chromosome fusion yet strikingly, these cells had sufficient telomere length and telomere DNA at the fusion sites [36, 38]. Following a number of yeast studies demonstrating a critical role of Ku at yeast telomeres [39, 40] it was demonstrated that Ku was present at the mammalian telomere [37, 41, 42]. The telomere/Ku complex is dependent upon the shelterin subunit TRF1, does not involve direct binding to TTAGGG telomeric repeat sequences [41, 43] and is independent of DNA-PK<sub>CS</sub>. Like Ku, DNA-PK<sub>CS</sub> is located at telomeres, has a role in telomere capping however does not affect either telomere length or telomerase activity, indicating that another function of DNA-PK<sub>CS</sub> is the protection of telomeric DNA and chromosome ends [34, 36, 38]. To date it is still unknown as to whether DNA-PK<sub>CS</sub> telomere recruitment is Ku-dependent and if DNA-PK<sub>CS</sub> role at the chromosome ends is structural. Furthermore the loss of DNA-PK<sub>CS</sub> has been shown to dramatically affect the rate of telomere loss in mice that lack both telomerase and DNA-PK<sub>CS</sub> compared to single knockout mice [44]. Additional studies revealed that this enhanced rate of telomere degradation was independent of Ku although the mechanistic relationship between DNA-PK<sub>CS</sub> and telomerase remains undefined [44].

As is clear, these cellular processes require a significant number of proteins and protein-protein complexes. Our cellular DSB repair pathways principally require ATM, the MRN protein complex, RPA, ATM- and *Rad3*-related (ATR), BRCA1, BRCA2 [45], Rad51, Rad52 Ku70/80, DNA-PK<sub>CS</sub>, Artemis and XRCC4.

### 3.4 The DNA Damage Response: Determining Cell Fate

In our cells the ability to repair DSBs is second only to the detection and response to DSBs. Within the cell DNA lesions are quickly recognized by the DNA damage response (DDR) proteins which activate cell cycle checkpoints and drive the repair process discussed previously. Depending on the nature and/or abundance of this damage different DNA repair pathways are involved, that together, form an extremely complex, interacting defense platform against genotoxic damage (summarized in Fig. 3.3). The DDR is a signal transduction pathway that is primarily mediated by proteins of the phosphatidylinositol 3-kinase-like protein kinases (PI3KKs) family many of which have been described in the repair of DSBs including, ATM, ATR and DNA-PK. In addition to these, there are also the poly (ADP) ribose polymerase (PARP) family. While there are 16 PARP family members, only PARP1 and PARP2 have been implicated in the DDR [46].

The DDR regulates all of the physiological processes that ultimately allow the cell to determine its fate; such as triggering apoptosis (programmed cell death), enter terminal differentiation via senescence (permanent cell cycle arrest) or to temporarily induce cell cycle arrest allowing DNA repair to occur. Taking into consideration the severity of these cellular choices a large proportion of the DDR is mediated by rapid post-translational protein modifications, such as phosphorylation or acetylation. While this is the case for the majority of the DDR signalling cascade,



**Fig. 3.3** DNA damage and repair

there is a proportion of this process that is mediated at the slower, transcription level, requiring various effector gene transcription and subsequent protein translation prior to their involvement in the DDR. This dual action allows information to be incorporated within the DDR over time. Upon recognition of DNA lesions ATM, ATR and/or DNA-PK initially phosphorylate mediator proteins (including themselves) which act to amplify the DDR recruiting additional substrates including (but

not exclusively) the Chk1, Chk2, p38 and MK2 kinases [47]. In addition to these, the most extensively studied component of the DDR is the tumour suppressor p53 which sits at the center of these signalling networks.

The transcription factor p53 is often referred to as “the guardian of the genome” as it is an essential regulator of the cellular response to stress and is crucial to the cellular DDR. Under normal physiological conditions the p53 protein is maintained at a low level by its negative regulator, the E3 ubiquitin ligase MDM2 that targets p53 for poly-ubiquitination and proteosomal degradation. However following the activation of the DDR, the p53-MDM2 interaction is disrupted and p53 is rapidly stabilized (following its initial phosphorylation at serine 15). The accumulated p53 protein can then undergo additional extensive post-translational modifications that includes further phosphorylation, acetylation, methylation, ubiquitination, sumoylation neddylation and glycosylation (reviewed extensively in [48]). Following DSB formation p53 is activated by ATM within a feedback loop that includes WIP1 phosphatase and MDM2, both of which are p53-regulated genes. This acts to turn off ATM and p53 respectively [49]. This temporal mechanism that activates p53-regulated gene expression in “waves” allows the cell to evaluate if the initiating damage has been repaired, suggesting that cell can obtain crucial cell fate information including the persistence of DNA damage, directing the cell to instigate apoptosis or senescence. This response is further enforced by the recognition of the DSB by the MRN complex, recruiting ATM and driving the HR process described previously. An important component of this process, highlighting the significant overlap within this cellular response is where DSB resection occurs after the RPA-DNA complex has formed. The recruitment of Rad51 to this complex, generates Rad51 filaments in a BCRA1-dependent manner driving HR. While this was considered to be exclusively ATM-dependent, Rad51 phosphorylation (by Chk1) is ATR-dependent [50] while BCRA2 itself is phosphorylated by ATR [51]. This indicates that both ATM and ATR are integral to the DNA repair and by their signalling to Chk1 and Chk2 potentially activate p53, allowing p53 to dictate cell fate.

It is widely accepted that p53 activation triggers either cell cycle arrest or apoptosis and that it is the transcriptional activation of p53-regulated genes that is essential for tumour suppression. However, understanding *how* p53 can direct specific cell fates still remains elusive.

While the role (s) of DNA-PK<sub>CS</sub> in NHEJ and the DDR are clear, the most contentious issue regarding DNA-PK<sub>CS</sub> function involves DNA-PK signalling following cellular stress via the tumour suppressor protein p53. The waters become further muddied when one examines the considerable research focused on p53 and the vast cross-talk between different signalling cascades principally mediated by p53. While it is clear p53 can function in a transcription independent manner (for a review see [52, 53]) the clearest understandings of p53 function are based around its transcriptional activity [54]. The fact that over half of all cancers contain specific p53 mutations [55], the attenuation of p53-mediated gene expression clearly indicates the importance of p53-dependent gene expression in tumour suppression. The crucial limitation to date is *how* p53 turns particular genes on or off and has been the focus of intensive research [56–61].

Both *in vitro* and *in vivo* investigations have produced conflicting results with respect to and the involvement of DNA-PK<sub>CS</sub> in the signalling cascade that links DNA damage detection to p53 activation. Following any type of DNA damage the cell is faced with the decision to induce cell cycle arrest or induce apoptosis. This is further complicated with the reports implicating a role of DNA-PK and Ku in cellular senescence and autophagy [62, 63]. The stabilization and activation (via post-translational modifications) of p53 is crucial for each of these cell fates. It is now widely accepted that DNA-PK<sub>CS</sub> phosphorylates Chk2 (at threonine 68) [64, 65] and p53 at two specific residues (serine 15 and serine 37) [66] and there has been recent evidence that DNA-PK<sub>CS</sub> phosphorylates p53 at serine 46 [67–69]. Despite this clear p53 activation the role of DNA-PK<sub>CS</sub> in p53 activation remained controversial particularly in regard to the p53-dependent induction of cell cycle arrest [70–75]. *In vivo* studies using DNA-PK<sub>CS</sub><sup>-/-</sup> mice categorically resolved this issue demonstrating that when absent, DNA-PK<sub>CS</sub><sup>-/-</sup> mice could still phosphorylate p53 at serine 18 (the murine equivalent of human serine 15) following gamma irradiation (IR) and that fibroblasts from the these treated animals would undergo cell cycle arrest [76]. Further, these same groups demonstrated that it was the related PI3KKs ATM and ATR that mediated this cellular response [76].

However, the ability to induce apoptosis following DNA damage is critical to prevent cancer development and to prevent aberrant DNA from being passed to daughter cells after cell division. While it is now clear that DNA-PK<sub>CS</sub> does not have a role in inducing cell cycle arrest (discussed above) there is now a significant body of data implicating DNA-PK<sub>CS</sub> in the apoptotic response to severe DNA damage. For example, following the over expression of protein kinase C $\delta$  normal cells mediate a robust apoptotic response. In contrast, DNA-PK<sub>CS</sub><sup>-/-</sup> cells are significantly more resistant to this method of apoptosis induction [77]. This observation is further supported by studies showing that IR induced apoptosis (a p53-dependent process) is significantly attenuated in DNA-PK<sub>CS</sub><sup>-/-</sup> mouse thymocytes [78]. Similarly following IR exposure E1A transformed fibroblasts mediate a potent p53-dependent apoptotic response that in the absence of DNA-PK<sub>CS</sub> was significantly attenuated [75, 79]. Concomitant to this observation, these DNA-PK<sub>CS</sub><sup>-/-</sup> fibroblasts show significantly reduced p53 induction and the absence of p53 serine 18 phosphorylation [75]. In addition to mediating post-translational modifications, this was the first article to report that DNA-PK and p53 could, under these specific apoptotic conditions form a protein-protein complex [79]. Since this report, this observation was also noted in human myeloid leukemia, pancreatic and colon cancer cell lines after gemcitabine, a novel deoxycytidine analogue and current cancer therapeutic [80, 81]. These results suggest that DNA-PK and p53 may form a sensor complex that could detect the disruption of DNA replication caused by nucleoside analogue incorporation and may subsequently signal for apoptosis. These observations in particular support a number of immunohistological studies that show following IR, that ATM, ATR, p53 binding protein (p53BP1) and histone 2 AX (H2AX) form distinct DNA damage foci at the sites of DNA damage in contrast to both p53 and DNA-PK<sub>CS</sub> that show a diffuse nuclear staining profile [82]. These studies suggest that a p53-dependent apoptotic response could be directed by DNA-PK<sub>CS</sub>. Interestingly it

has recently been shown that the p53-dependent apoptotic program requires (in addition to serine 15) serine 46 phosphorylation [83] a novel putative DNA-PK<sub>CS</sub> target residue [69]. Strengthening the case further, DNA-PK<sub>CS</sub> was shown to phosphorylate H2AX [84], a hallmark of apoptosis induction (for a detailed review see [85]). This report demonstrated that DNA-PK remained active in late apoptotic cells and that when active DNA-PK is able to initiate an early step in the DDR. DNA-PK<sub>CS</sub> has also been shown to negatively regulates *p21* expression by directly interacting with the p21 transcription machinery via p53, thus priming the cell to induce apoptosis following cellular stress [81]. Recently it has been reported that the mechanism of killing during HIV viral integration is DNA-PK-dependent and activated (via phosphorylation) p53 and histone H2AX [86, 87]. Another study demonstrated that under cellular conditions that induced apoptosis, the inhibition of DNA-PK<sub>CS</sub> prevented p53 phosphorylation and accumulation, significantly reduced caspase-3 cleavage and attenuated the overall cellular apoptotic program [68]. Furthermore Ku70 was shown to accumulate after IR treatment and bound XIP8 correlating with reduced cell growth and elevated cell death [88]. The link between Ku70 and cell death is also noted in a neurodegenerative disease models where DNA-PK<sub>CS</sub> links DNA damage to Bax-dependent excitotoxic cell death, by phosphorylating Ku70 on serines 6 and/or 51, initiating Bax translocation to the mitochondria and directly activating a pro-apoptotic Bax-dependent death cascade [89]. These reports complement the described role of DNA-PK particularly in regard to the maintenance of chromosomes. As previously considered, telomerase deficient (*Terc*<sup>-/-</sup>) mice show widespread germ cell line apoptosis however a *Terc*<sup>-/-</sup>DNA-PK<sub>CS</sub><sup>-/-</sup> double knockout mouse strain does not show increased apoptosis indicating a clear role in mediating apoptosis (that is independent of Ku) in cell lines with critically shortened telomeres [44, 90, 91].

### 3.5 The Clinical Significance

The loss of genomic integrity due to the loss or inactivation of DDR genes enhances the risk that cells will accumulate additional mutations that promote cancer development. This is strongly supported in data from several cancer types where the somatic mutations in DDR are routinely observed (summarised in Table 3.1). This is a significant component of many cancers in particular breast cancer where germ-line mutations in the DSB repair genes *BRCA1* and *BRCA2* significantly predispose carriers to developing breast and ovarian cancers. Similarly mutations in *TP53* (a core component of the DDR) significantly predispose carries to childhood osteosarcoma, breast, brain, leukaemia and adrenocortical carcinomas. In addition to significantly increasing the predisposition to various cancers, mutations within the DDR also dramatically affect the sensitivity of tumours to chemotherapy. This has been most robustly demonstrated in HR and DSB repair deficiency where *BRCA*-deficient tumours are extremely sensitive to PARP inhibition. Clearly this is a double edged sword, while HR deficiencies could be effectively targeted by

**Table 3.1** Hereditary cancer syndromes

Syndrome	Gene(s) mutated	clinical presentation	mode of inheritance
Fanconi anemia aplastic anemia, Myelodysplastic syndrome, Acute myeloid leukemia	<i>FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCL, FANCM, FANCN, FANCO, FANCP and BRCA2</i>	Hepatic tumors and squamous cell carcinomas of the esophagus, oropharynx and uvula commonly present.	Autosomal dominant
Familial adenomatous polyposis	<i>APC</i>	Colorectal cancer	Autosomal dominant
Hereditary breast-ovarian cancer syndrome	<i>BRCA1, BRCA2</i>	Breast and ovarian cancer.	Autosomal dominant
Hereditary non-polyposis colon cancer (Lynch syndrome)	<i>MLH1, MSH2, MSH6 and PMS2</i>	Colorectal, endometrial cancer, stomach cancer, ovarian cancer, cancers of the small bowel and pancreatic cancer.	Autosomal dominant
Hereditary paraganglioma-pheochromocytoma syndrome	succinate dehydrogenase subunit genes, <i>SDHD, SDHA, SDHB, SDHC, SDHE</i>	Neuroendocrine tumours	Autosomal dominant
Li-Fraumeni syndrome	<i>TP53</i>	Soft tissue sarcomas, osteosarcoma, breast cancer, brain cancer, leukaemia and adrenocortical carcinoma	Autosomal dominant
MUTYH (mutY Homolog (E. coli))-associated polyposis	<i>MUTYH</i>	Colorectal cancer, gastric adenomas and duodenal adenomas	Autosomal recessive
Nevoid/Gorlin syndrome	<i>PTCH</i>	Significant increase in basal cell carcinoma susceptibility	Autosomal dominant
Von Hippel-Lindau	<i>Von Hippel-Lindau</i>	Central nervous system and retinal hemangioblastomas, clear cell renal carcinomas, pheochromocytomas, pancreatic neuroendocrine tumours, pancreatic cysts, endolymphatic sac tumors and epididymal papillary adenomas	Autosomal dominant
Xeroderma pigmentosum (XPC)	<i>XPA, XPB, XPC, XPD, XPE, XPF, XPG and Pol η</i>	Melanoma (10,000 fold susceptibility increase)	Autosomal recessive
Ataxia telangiectasia (AT)	<i>ATM</i>	Increased risk for breast cancer, leukemias and lymphomas, T-ALL, atypical B cell chronic lymphocytic leukemia, and T-PLL	Autosomal recessive
Severe combined immunodeficiency (SCID)	<i>DNA-PK</i>	Significantly elevated lymphoid malignancy risk	Autosomal recessive
Rothmund-Thomson syndrome (RTS)	<i>RECQL4</i>	Osteosarcoma	Autosomal recessive
Wilms' tumour	<i>WT1</i>	Nephroblastoma	Autosomal dominant

DSB-inducing chemotherapeutics, the genomic instability that enables the acquisition of additional mutations that could increase therapy resistance further. When treating cancer, the most significant aspect associated with chemotherapy are side-effects resulting from non-specific targeting to normal non-cancerous cell and poor efficacy as a result of intrinsic (such as mutated p53) or acquired drug resistance, such as a cellular change affecting drug metabolism or uptake. These aspects are considered in more detail in chapter W.LINK.

### 3.6 Future Directions

The cell cycle, DNA replication and the recognition and repair of DNA damage are three of the most complicated and elegantly controlled systems within our cells. It is clear that the CDKs, cyclins, CDKs are crucial for the temporal and high fidelity transmission of genetic information into daughter progeny cells. In tandem with this critical process, these proteins have been implicated in functions far beyond the cell cycle (and scope of this chapter, reviewed in [92]. Concomitant to the importance of genome preservation, our cells have evolved a number of highly complex recognition and repair processes to resolve DSBs providing a critical defense platform to preserve genomic integrity. As part of this platform, our cells contain crucial multi-protein complexes including PI3KKs and signaling intermediates that enable p53 to direct the cellular choice between life (transient cell cycle arrest or senescence) or death (apoptosis). The importance of these proteins and signaling cascades is apparent when one considers the hereditary predisposition to a broad range of cancers when they are mutated or the genetic instability that they promote when mutations within these genes are acquired. Understanding the relationship between ATM, ATR, DNA-PK<sub>CS</sub> and p53 as well as the specific cellular signals that activate these components needs to be further examined. This leads to the crucial questions of how are these DSB signals evaluated and acted on by p53 and if there is a particular p53-modification code that could induce arrest versus apoptosis?

As our understanding of the DDR pathways continues to increase and become more refined, these offer rich areas to exploit therapeutically and while targeting (for example) HR defective tumours with PARP inhibitors is highly effective, the molecular screening of patient tumours is vital prior to treatment. Continued research is vital to enhance our understanding of the cell cycle, DSB signalling and tumour suppression is crucial if we are to specifically sensitise cancer cells to new therapeutic approaches.

#### Multiple Choice and Shot Answer Questions

1. During the cell cycle, the phase where the cell increases in size is termed the
  - (a) **Gap 1/G<sub>1</sub> phase**
  - (b) Synthesis/S phase
  - (c) Gap 2/G<sub>2</sub> phase
  - (d) Mitosis/M phase.

*“The second phase is G 1 (or Gap 1) where the cell increases in size” page 30*



2. Cyclin-dependent kinase inhibitors (CDKI) are divided into classes. These are
- Ink4/CIP
  - CIP/KIP
  - KIP/Ink4
  - Ink4, CIP/KIP**

*“The CDKIs are divided into two classes (that is based on their Cdk specificity and structure). The first class are the Ink4 members (p16<sup>INK4a</sup> [Cdkn2a], p15<sup>INK4b</sup> [Cdkn2c], p18<sup>INK4c</sup> [Cdkn2c] and p19<sup>INK4d</sup> [Cdkn2d]) that predominantly target Cdk4 and Cdk6. The second class are the Cip/Kip family members (p21<sup>CIP1</sup> [Cdkn1a], p27<sup>Kip1</sup> [Cdkn1b] and p57<sup>KIP2</sup> [Cdkn1c]) that target cyclin D-, E-, A- and B-dependent kinase complexes.” Page 30*

3. During G<sub>2</sub>/M, CyclinB binds to
- CDK4/5
  - CDK2
  - CDK1**
  - CDK1 and CDK2

Shown in Fig. 3.1 (Page 31)

4. How many systems do mammalian cells have to repair double strand breaks?
- 1
  - 2
  - 3**
  - 4

Shown in Fig. 3.2 (page 32)

5. Which double strand break repair process results in the formation of a Holiday junction?

### **Homologous Recombination**

Shown in Fig. 3.2 (middle right of page 32).

6. Which double strand break repair process is initiated by the binding of Ku70 and Ku80?

### **Non-homologous End-joining (NHEJ)**

*“In NHEJ repair, each broken DNA end is first bound by one Ku70/80 heterodimer, and two heterodimers must come together to bridge matching ends [9] ensuring high fidelity ligation” (Page 34)*

7. Homologous recombination requires an intact sister chromatid, as such, its use is therefore restricted to which phase(s) of the cell cycle?
- G<sub>1</sub> and M
  - G<sub>2</sub> and G<sub>1</sub>
  - S
  - S and G<sub>2</sub>**

*“Whether HR (or NHEJ) is used to repair double-strand breaks is largely determined by the phase of cell cycle. As HR requires an intact sister chromatid it is restricted to the S and G 2 phases of the cell cycle [7].” (Page 33)*

8. The MRN complex recruits which PI3KK protein to the double strand break?
- (a) ATR
  - (b) **ATM**
  - (c) DNA-PK<sub>cs</sub>
  - (d) ARTEMIS

*“The MRN complex recruits the Ataxiatelangiectasia mutated (ATM) protein as well as the Sae2 protein to mediate signal transduction and generate these short 3' overhangs of single-strand DNA.” (Page 33)*

9. The tumour suppressor p53 is maintained under non-DNA damage conditions by which protein?
- (a) Chk1
  - (b) Chk2
  - (c) BCRA1
  - (d) **MDM2**

*“Under normal physiological conditions the p53 protein is maintained at a low level by its negative regulator, the E3 ubiquitin ligase MDM2 that targets p53 for poly-ubiquitination and proteosomal degradation.” (Page 37)*

10. Which of the following PI3KKs are capable of directing a cell cycle arrest response following DNA damage?
- (a) ATM and DNA-PK<sub>CS</sub>
  - (b) ATR and DNA-PK<sub>CS</sub>
  - (c) **ATM and ATR**
  - (d) ATM

*“In vivo studies using DNA-PK CS-/- mice categorically resolved this issue demonstrating that when absent, DNA-PK CS -/- mice could still phosphorylate p53 at serine 18 (the murine equivalent of human serine 15) following gamma irradiation (IR) and that fibroblasts from these treated animals would undergo cell cycle arrest [70]. Further, these same groups demonstrated that it was the related PI3KKs ATM and ATR that mediated this cellular response [70].” (Page 38)*

11. Which PI3KK protein has been implicated in cell death following HIV-integration?
- (a) ATM
  - (b) ATR
  - (c) **DNA-PK<sub>CS</sub>**
  - (d) ATM and ATR

*“Recently it has been reported that the mechanism of killing during HIV viral integration is DNA-PK-dependent and activated (via phosphorylation) p53 and histone H2AX [80, 81].” (Page 39)*

12. Which of the following proteins are pro-apoptotic?
- (a) Bcl2, p21, PUMA, Bax
  - (b) Bax, MDM2, 14-3-3 $\sigma$ , NOXA
  - (c) **Bax, PUMA, NOXA, p53AIP1**
  - (d) p38, p21, p53AIP1, Bax

Figure 3.3 (Page 36)

13. When bound by 14-3-3 $\sigma$ , Cdc25 inhibits
- (a) cyclinE
  - (b) cyclinA
  - (c) cyclinB
  - (d) **cyclinE, cyclinA, cyclinB**
  - (e) none of the above

Shown in Fig. 3.3 (Page 36)

14. Which of the following PI3KK is involved in telomere end capping?
- (a) ATM
  - (b) ATR
  - (c) **DNA-PK<sub>CS</sub>**
  - (d) ATRIP

*“DNA-PK<sub>CS</sub> is located at telomeres, has a role in telomere capping however does not affect either telomere length or telomerase activity, indicating that another function of DNA-PK<sub>CS</sub> is the protection of telomeric DNA and chromosome ends [33, 35, 37]” (Page 35)*

15. Which of the following are not mediator proteins within the double strand repair processes in mammalian cells?
- (a) p38
  - (b) Chk1
  - (c) Chk2
  - (d) **Mre11**

Shown in Fig. 3.3 (page 36)

16. Which of the following proteins are not instigator proteins within the mammalian DNA double strand repair processes?
- (a) Ku70
  - (b) Ku80
  - (c) **p53**
  - (d) Rad51

Shown in Fig. 3.3 (page 36) and described extensively throughout page 37.

17. Li-Fraumeni syndrome is an autosomal dominant condition caused by mutations within which gene(s)?
- (a) ***TP53***
  - (b) *BRCA1*
  - (c) *PTCH*
  - (d) *FANCA*

Shown in Table 3.1 (and described in Sect. 3.5).

18. *BRCA1* and *BRCA2* mutations are commonly associated with predisposition to which cancers?
- (a) Osteosarcoma and breast
  - (b) **Breast and ovarian**
  - (c) Melanoma and ovarian
  - (d) Leukaemia and osteosarcoma

Shown in Table 3.1

19. Mutations within *PTCH* result in which genetic condition?
- (a) Familial adenomatous polyposis
  - (b) Von Hippel-Lindau
  - (c) Xeroderma pigmentosum
  - (d) **Nevoid/Gorlin syndrome**

Shown in Table 3.1 (and described in Sect. 3.5).

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# Chapter 4

## Tumour Angiogenesis



Patrícia Alexandra Madureira

**Abstract** It has been over 40 years since Judah Folkman published his classic article in the *New England Journal of Medicine*, entitled “Tumor angiogenesis: therapeutic implications” (Folkman J. *N Engl J Med* 285:1182–1186, 1971). At the time Folkman proposed three bold postulates: (i) angiogenesis is essential for tumour growth beyond minimal size; (ii) tumours secrete a “tumor angiogenesis factor” that is responsible for inducing angiogenesis; and (iii) anti-angiogenesis is a potential cancer therapeutic strategy. After many years of controversy and scientific research progress these three postulates are currently widely accepted by the scientific community. Even though huge progress has been made regarding the identification and characterization of the molecular mechanisms that regulate tumour angiogenesis, anti-angiogenic therapy has not been as successful as originally anticipated.

**Keywords** Angiogenesis · VEGF · Hypoxia · Hypoxia Inducible Factor (HIF) · Glycolytic metabolism

It has been over 40 years since Judah Folkman published his classic article in the *New England Journal of Medicine*, entitled “Tumor angiogenesis: therapeutic implications” [1]. At the time Folkman proposed three bold postulates: (i) angiogenesis is essential for tumour growth beyond minimal size; (ii) tumours secrete a “tumor angiogenesis factor” that is responsible for inducing angiogenesis; and (iii) anti-angiogenesis is a potential cancer therapeutic strategy. After many years of controversy and scientific research progress these three postulates are currently widely accepted by the scientific community. Even though huge progress has been made regarding the identification and characterization of the molecular mechanisms that regulate tumour angiogenesis, anti-angiogenic therapy has not been as successful as originally anticipated.

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## 4.1 Tumour Hypoxia and the Angiogenic Switch

Approximately 90% of all human tumours are of epithelial origin. Most epithelial tissues are essentially large sheets of cells covering the body and lining the outside of organs. Epithelium also forms most of the glandular tissue in our body.

Epithelial cells derive from all three major embryonic layers. The epithelia lining the skin, parts of the mouth and nose, and the anus develop from the ectoderm; while cells lining the airways and most of the digestive system originate from the endoderm. The epithelium that lines vessels in the lymphatic and cardiovascular system derives from the mesoderm and is called endothelium.

Epithelial tissue is avascular, meaning that no blood vessels cross the basement membrane to enter the tissue, and for this reason nutrients and oxygen must diffuse from the underlying connective tissue to allow epithelial cell growth and survival. For this reason, in the absence of angiogenesis, tumours can only grow until they reach 0.2 mm in diameter, since this is the maximum distance for oxygen diffusion [2].

The main cause of tumour hypoxia prior to angiogenesis is the increasing distance between the growing tumour and the pre-existing blood vessels. Subsequent to angiogenesis, the abnormal function and structure of the newly formed blood vessels can originate hypoxic cores due to collapse, hypoperfusion and/or low oxygen transport. Also, other disease(s) or chemotherapy can lower the oxygen content in the patient's blood leading to hypoxia [2].

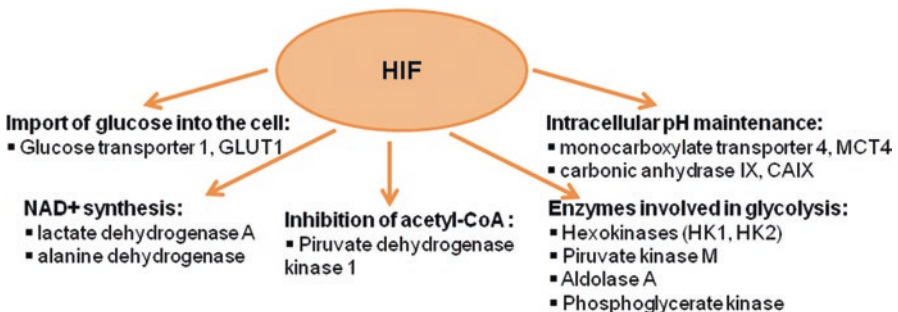
## 4.2 Hypoxia Inducible Factor (HIF) as a Key Regulator of the Hypoxic Response

The tumour hypoxic response is largely regulated by the transcription factor, Hypoxia inducible factor (HIF). HIF is a heterodimeric transcription factor, composed of an alpha subunit, HIF alpha (HIF- $\alpha$ ) and a beta subunit, HIF beta (HIF- $\beta$ ). There are three distinct HIF- $\alpha$  isoforms in mammals, namely HIF-1 $\alpha$ , HIF-2 $\alpha$  and HIF-3 $\alpha$  and one HIF- $\beta$  subunit, HIF-1 $\beta$ . While HIF-1 $\alpha$  is ubiquitously expressed, the expression of HIF-2 $\alpha$  and HIF-3 $\alpha$  is observed in endothelial cells, cardiomyocytes, interstitial cells of the kidneys, liver parenchyma, type 2 pneumocytes and myeloid cells [3, 4]. The HIF-1 $\beta$  subunit is constitutively expressed in cells, while HIF- $\alpha$  is rapidly degraded in oxygenated cells. For this reason, HIF transcriptional activity is highly regulated through the stabilization of the HIF- $\alpha$  subunit which occurs under hypoxic/ low oxygen conditions. In the presence of oxygen, the enzymes prolyl hydroxylases (PHD) add hydroxyl groups to two proline residues of HIF- $\alpha$ . This modification allows binding of the ubiquitin ligase protein, Von Hindel Lindau (VHL), to HIF- $\alpha$  and the subsequent ubiquitination and degradation of HIF- $\alpha$  via the proteasome [5]. Additionally, another mechanism of HIF- $\alpha$  regulation is mediated by the factor inhibiting HIF (FIH). FIH hydroxylates a residue of asparagine within the C-terminal region of HIF- $\alpha$ , blocking the binding of transcriptional factors, such as CBP/p300 to this domain and inhibiting in this way HIF mediated transcription [6, 7].

Under hypoxic conditions, HIF- $\alpha$  hydroxylation does not occur since both PHD and FIH functions as well as the hydroxylation reaction are oxygen dependent. Consequently, HIF- $\alpha$  rapidly accumulates and translocates into the nucleus, where it binds to the HIF-1 $\beta$  subunit and its co-activators CBP/p300, constituting a functionally active HIF transcription factor. The HIF heterodimers recognize and bind to hypoxia response elements (HREs) in the genome, which are similar to Enhancer box (E-box) motifs and have the consensus sequence 5'-G/ACGTG-3' [8]. HIF is the main regulator of the cellular response to hypoxia, inducing the transcription of over one hundred genes involved in critical processes, such as angiogenesis, alteration of cellular metabolism, cellular pH regulation, cell survival, migration, invasion, epithelial-mesenchymal transition and cell proliferation [9–12].

### 4.3 Hypoxia Induced Changes in Cellular Metabolism

To survive in a hypoxic/ low oxygen environment it is absolutely crucial for the cancer cell to alter its aerobic respiration metabolism that although very efficient at the energy level, relies on the availability of high concentrations of intracellular oxygen, to a glycolytic metabolism, virtually independent of oxygen. Stabilization of the transcription factor HIF in low oxygen conditions leads to the transcription of a large number of genes that encode for proteins involved in promoting the glycolytic pathway, such as proteins that stimulate the import of glucose into the cell (e.g. glucose transporter 1, GLUT1); enzymes involved in the glycolytic pathway (e.g. hexokinases (HK1, HK2), piruvate kinase M; aldolase A; phosphoglycerate kinase); proteins that inhibit the production of acetyl-CoA (e.g. piruvate dehydrogenase kinase 1) which is necessary for the tricarboxylic acid cycle (TCA cycle), diverting carbon away from the mitochondria and suppressing O<sub>2</sub> consumption; activation of mechanisms that lead to NAD<sup>+</sup> synthesis for glycolysis (e.g. lactate dehydrogenase A; alanine dehydrogenase) and activation of mechanisms for intracellular pH



**Fig. 4.1** Induction of glycolysis by HIF. Stabilization of the transcription factor HIF in low oxygen conditions leads to the transcription of a large number of genes that encode for proteins involved in promoting the glycolytic pathway as shown in the figure

maintenance (e.g. monocarboxylate transporter 4, MCT4; carbonic anhydrase IX, CAIX) [10, 13] (Fig. 4.1).

Even though glycolysis is not nearly as efficient as aerobic respiration regarding energy production, it does provide other advantages to the cancer cell. The glycolytic intermediaries can be readily used for the biosynthesis of DNA, RNA, lipid and aminoacids/ proteins which are critical processes in fast proliferating cells such as cancer cells [14]. In addition the glycolytic metabolism renders cancer cells independent of oxygen availability within the tumour mass, which can be very variable with the progression of the tumour.

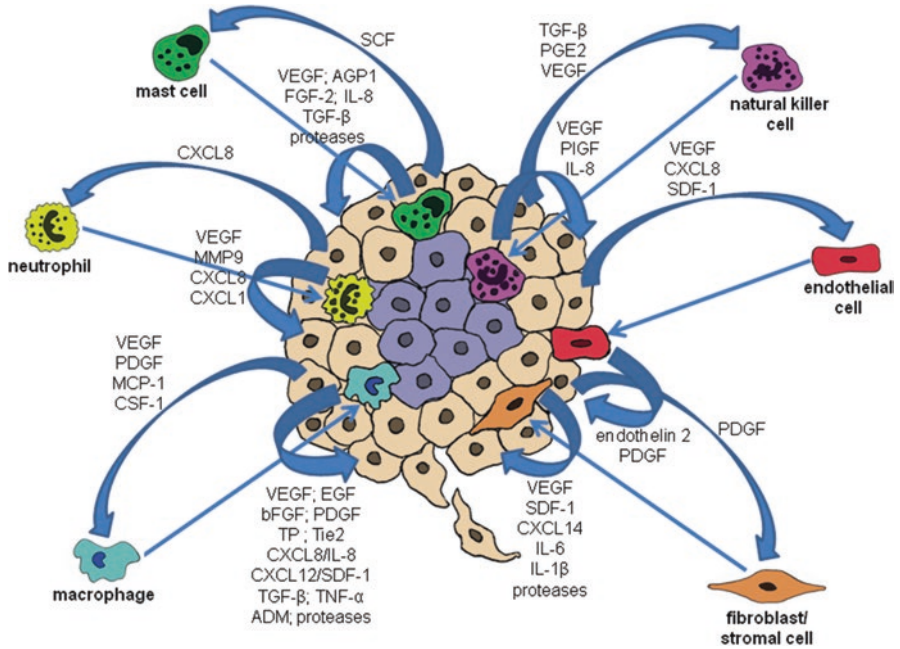
#### 4.4 Hypoxia Induced Tumour Angiogenesis

Another critical response, essential for tumour survival under hypoxic conditions is the formation of new blood vessels, which will provide oxygen and nutrients that are essential for tumour survival and growth, a process known as tumour angiogenesis,.

HIF induces the transcription of *vascular endothelial growth factor (VEGF)*, *platelet derived growth factor (PDGF)*, *angiopoietin* and *eritropoietin* genes that are involved in the promotion of angiogenesis [9, 15–18]. VEGF is particularly important in tumour angiogenesis, being highly secreted not only by cancer cells, but also by tumour associated cells such as macrophages and other immune cells, as well as cancer associated fibroblasts (CAFs) (reviewed in detail bellow). VEGF binds to the VEGF receptor (VEGFR) at the surface of endothelial cells which constitute the internal layer of the blood vessels, stimulating in this way endothelial cell proliferation, survival, secretion of matrix degradation enzymes (e.g. matrix metalloproteases and plasmin) and migration to the tumour site [9] (Fig. 4.2).

#### 4.5 The VEGF Family of Pro-angiogenic Proteins

Taken into account the complexity of the process of angiogenesis (described in detail bellow), it is remarkable that a single growth factor, VEGF, regulates this process so predominantly. The human genome contains five genes encoding for distinct VEGF family members, namely VEGF (also called VEGF-A), placenta growth factor (PlGF), VEGF-B, VEGF-C and VEGF-D. Structurally, the VEGF family of proteins are homodimers, constituted by two subunits of about 120 to 200 amino acids in length [19]. The VEGF family distinguishes itself from other angiogenic protein families by the fact that its members have largely non-redundant functions. VEGF is the main component of this family, and it stimulates angiogenesis both in physiological and pathological processes by signalling through the VEGF receptor-2 (VEGFR-2, also known as FLK1) [20, 21]. In contrast to VEGF, PlGF and VEGF-B appear to have a relatively minor role in the regulation of



**Fig. 4.2** The role of paracrine signalling between cancer cells and tumour associated cells (micro-environment) in tumour angiogenesis. Tumour cells secrete proteins that function as chemoattractants to tumour associated cells, such as macrophages, neutrophils, mast cells, natural killer cells, endothelial cells and fibroblasts/ stromal cells. Recruited tumour associated cells in their turn secrete proteins that will further stimulate cancer cell growth/ proliferation, tumour angiogenesis and recruitment of cells to the tumour site

angiogenesis, but have been shown to play a role in cardiac muscle function [22, 23]. VEGF-C, a ligand of the VEGFR-2 and VEGFR-3 receptors, activates blood-vessel tip cells [24, 25]. VEGFR-3 activation by VEGF-C has been shown to lead to the formation of blood vessels during early embryogenesis, but later becomes a key regulator of lymphatic angiogenesis—the formation of new lymphatic vessels from pre-existing vasculature [26]. VEGF-D binds to VEGFR-3 and is also involved in lymphatic angiogenesis [24].

### 4.6 The Mechanism of Angiogenesis

In the developing mammalian embryo, angioblasts differentiate into endothelial cells, which assemble into a vascular labyrinth, a process known as vasculogenesis. Distinct signals stipulate arterial or venous differentiation. Subsequent sprouting, known as angiogenesis, ensures expansion of the vascular network. Arteriogenesis then occurs, in which endothelial cell channels become covered by

pericytes or vascular smooth muscle cells, which provide structure and regulate perfusion [2, 27].

Angiogenesis is a critical mechanism during embryonic development and under certain physiological circumstances in the adult, such as wound healing and formation of placenta during pregnancy [28, 29]. Angiogenesis is a complex process that is highly mediated by the endothelial cells that line the blood vessels [30].

In a fully developed (adult) mammal, when a quiescent vessel senses an angiogenic signal, pericytes detach from the vessel wall and set free from the basement membrane via proteolytic degradation mediated by matrix metalloproteases. Endothelial cells then loosen their junctions, and the nascent vessel dilates. VEGF increases the permeability of the endothelial cell layer, causing plasma proteins to extravasate from the vessel and to lay down a provisional extracellular matrix (ECM) scaffold. In response to integrin signalling, endothelial cells migrate onto this ECM surface. Proteases release angiogenic molecules stored in the ECM such as VEGF and FGF and also remodel the ECM. To build a perfused tube and prevent endothelial cells from moving all together in a deregulated fashion towards the angiogenic signal, one endothelial cell, named the tip cell, becomes selected to lead the tip in the presence of factors such as VEGF receptors, neuropilins and the NOTCH ligands, DLL4 and JAGGED1. Cells neighbouring the tip cell assume subsidiary positions as stalk cells, and divide to elongate the stalk [stimulated by NOTCH, NOTCH-regulated ankyrin repeat protein (NRARP), Wnt, PlGF and fibroblast growth factor (FGF)] and to establish the lumen of the blood vessel (mediated by VE-cadherin, CD34, sialomucins, VEGF and hedgehog) [31]. While tip cells have filopodia to sense environmental guidance cues such as ephrins and semaphorins, stalk cells release molecules such as EGF-like domain-containing protein 7 (EGFL7) into the ECM to convey spatial information about the position of their neighbours and to elongate the stalk [31]. Changes that occur in endothelial cell interactions with the ECM, as well as changes in cell-to-cell interactions are essential for the angiogenic process. Endothelial cells are linked to each other by tight and adherens-type junctions and are linked to the extracellular matrix by a variety of integrins and other adhesion molecules [32]. VEGF activates endothelial cells, in part through stimulating signal transduction pathways that regulate the enzymatic components of adhesion complexes. VEGF-induced tyrosine phosphorylation of VE-cadherins, a component of adherens-type cell-to-cell junctions, has been implicated as a key step in endothelial cell migration [33]. Experimental evidence supporting a role for VEGF in regulating cell-to-matrix interactions includes the findings that VEGF enhances the expression of integrins, and that neutralizing antibodies to  $\alpha 5$  integrins block growth factor induced neovascularization [34, 35]. For a blood vessel to be perfectly functional, it must become mature and stable. Endothelial cells return to their quiescent state, and signals such as platelet-derived growth factor B (PDGF-B), angiopoietin 1 (ANG-1), transforming growth factor- $\beta$  (TGF- $\beta$ ), ephrin-B2 and NOTCH induce the coverage of the newly formed blood vessel with pericytes and smooth muscle cells. Protease inhibitors known as tissue

inhibitors of metalloproteases (TIMPs) and plasminogen activator inhibitor-1 (PAI-1) cause the deposition of a basement membrane and junctions are re-established to ensure optimal flow distribution. Under normal circumstances, vessels regress if they are unable to become perfused [31].

Normal angiogenesis is an extremely tightly regulated process involving not only a large number of stimulators, but also and very importantly inhibitors such as thrombospondin-1 (Tsp-1), angiostatin and endostatin [36–38]. Tsp-1 is a key negative regulator of angiogenesis inducing endothelial cell apoptosis, inhibiting migration and down regulating VEGF expression [39–43]. Angiostatin is a degradation product of plasminogen (Plg), constituted by kringles 1–3 of Plg. Angiostatin binds to proteins expressed on the surface of endothelial cells, such as annexin A2 heterotetramer (AIIIt), angiomin, integrin  $\alpha v \beta 3$ , c-met and ATP synthase functioning as a negative regulator of these proteins and consequently inhibiting angiogenesis [44]. Endostatin is a 20-kDa C-terminal globular domain of collagen XVIII. A number of mechanisms have been proposed for endostatin anti-angiogenic activity, such as inhibition of phosphorylation of focal adhesion kinase (FAK) via binding to integrin  $\alpha 5 \beta 1$ , blockage of VEGF and Wnt signalling and binding and inactivation of metalloproteases [45].

## 4.7 Normal Versus Tumour Angiogenesis

Tumour angiogenesis is very different from normal angiogenesis in the sense that there is an excess of pro-angiogenic signalling that stimulate endothelial cell proliferation and migration, which is not accompanied by signals that lead to the recruitment and proliferation of pericytes and smooth muscle cells. Also, in tumour angiogenesis the regulatory mechanisms that are responsible for “shutting down” neovascularisation in healthy tissues do not function normally. Angiogenesis inhibition in tumours is usually compromised since the transcription of the *THBS1* gene that encodes for Tsp-1 is commonly impaired. *THBS1* transcription is strongly induced by p53 [46]. Conversely, the loss of p53 function, observed in a large percentage of human tumours, leads to a substantial decrease in Tsp-1 protein expression within the tumour mass [47]. Oncogenes such as Myc, Ras, Src and Jun function in the opposite way inhibiting the transcription of the *THBS1* gene [48–52]. Since constitutive activation of these oncogenes is frequently observed in tumours, this results in the inhibition of Tsp-1 protein expression and consequently also contributes substantially to the inhibition of anti-angiogenic mechanisms in cancer patients. As a consequence of the excessive pro-angiogenic signalling in conjunction with inhibition of anti-angiogenic mechanisms, tumour vasculature is marked by precocious capillary sprouting, convoluted and excessive vessel branching, distorted/ poorly structured and enlarged vessels, erratic blood flow, microhemorrhage, “leakiness” leading to accumulation of plasma in tissue areas close or inside the tumour, vessel collapse (which can create new hypoxic cores within the tumour) and abnormal levels of endothelial cell proliferation and apoptosis [53, 54].

## 4.8 The Role of Tumour Associated Cells in Angiogenesis

Presently it is widely recognized that tumour progression is not only the result of accumulating genetic alterations in cancer cells, and that the tumour microenvironment plays a key role in different aspects of tumorigenesis. The exacerbated pro-angiogenic signalling observed in tumours, particularly during hypoxia is not only due to signals coming from the cancer cells, but especially due to interactions between cancer cells, endothelial cells and tumour associated cells, such as macrophages and stromal cells which are crucial for tumour angiogenesis. Various angiogenic molecules produced by either cancer cells or tumour associated cells can directly bind to their cognate receptors on endothelial cells and thus initiate angiogenesis. Thus, a paracrine regulation of angiogenesis by secreted proteins is well-recognized.

For instance, VEGF secreted by the cancer cells will not only stimulate endothelial cell proliferation, but will also act as a chemoattractant for macrophages. Other growth factors including endothelin 2 secreted by endothelial cells and platelet-derived growth factor (PDGF), macrophage chemoattractant protein 1 (MCP-1) and colony-stimulating factor-1 (CSF-1) secreted by cancer cells and released from the ECM have also been reported to promote monocyte/macrophage recruitment to the tumour site [55, 56]. Macrophages constitute a major component of the tumour mass, where they are commonly termed tumour associated macrophages (TAMs). Macrophages shift their functional phenotypes in response to various microenvironmental signals generated by cancer and stromal cells. During tumour initiation, tumour-infiltrating macrophages usually show an M1 phenotype (IL-12<sup>high</sup> IL-10<sup>low</sup>), but at late-stage tumour progression, TAMs generally switch to an M2 subset characterized by the IL-12<sup>low</sup> IL-10<sup>high</sup> phenotype [57]. Such TAMs (M2 subset) have been shown to provide a favourable microenvironment for tumour growth, survival and angiogenesis [58–60]. TAMs are recruited into hypoxic or necrotic areas of the tumour where they remove the tissue debris and stimulate repair processes [61, 62]. TAMs secrete a wide range of pro-angiogenic mediators, the most important of which being VEGF, but also including epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), PDGF, thymidine phosphorylase (TP), angiopoietin receptor Tie2, angiogenic CXC chemokines (CXCL8/IL-8 and CXCL12, also known as stromal derived factor-1, SDF-1), angiogenesis-associated factors such as transforming growth factor beta (TGF- $\beta$ ), tumour necrosis factor alpha (TNF- $\alpha$ ) and adrenomedullin (ADM), further promoting tumour angiogenesis [59, 63–66]. TAMs also secrete proteolytic enzymes such as plasmin, urokinase-type plasminogen activator (uPA) (activator of the protease plasmin), and metalloproteases, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12, whose combined action induces degradation of the basement membrane and ECM components, release of sequestered growth factors from the ECM, destabilization of the vasculature as well as migration and proliferation of endothelial cells contributing significantly in this way to tumour angiogenesis [59, 66–69].



Neutrophils inflammatory cells have also been shown to infiltrate tumours and promote angiogenesis [70]. CXCL8, which is abundantly produced by tumour cells, represents a potent chemoattractant for the recruitment of neutrophils to the tumour mass. CXCL8 is also associated with angiogenesis by directly activating the CXCR2 receptor on endothelial cells [71]. Activated neutrophils secrete VEGF, metalloproteases that degrade and remodel the ECM (e.g. MMP9) and chemokines, CXCL8 and CXCL1 contributing to tumour angiogenesis [72–74].

Natural killer (NK) cells are also recruited to the tumour site. The tumour micro-environment is able to affect NK functionality by a wide array of cytokines and soluble factors (e.g. TGF- $\beta$ , prostaglandin E2 (PGE2), VEGF), that act either inhibit their cytotoxic function or promote a pro-tumourigenic and pro-angiogenic phenotype [75, 76]. Recent reports have shown that tumour infiltrating NK cells produce elevated levels of VEGF, PlGF, IL-8 and induce endothelial cells chemotaxis and tube formation [76].

The recruitment and activation of mast cells (MCs, also known as mastocytes) to the tumour site has been shown to be mainly mediated by tumour-derived stem cell factor (SCF) and its receptor c-kit on MCs [77]. Mast cells contribute to the angiogenic switch in tumours through the production of diverse pro-angiogenic growth factors, cytokines and chemokines, including VEGF, angiopoietin-1, FGF-2, IL-8 and TGF- $\beta$  among others [78, 79]. Proteases produced by mast cells, such as trypsin, chymase, cathepsin G, elastase and collagenase, promote angiogenesis and are currently becoming targets for anti-angiogenic therapy [78, 80–83].

The fibroblasts within the tumour mass, also known as cancer-associated fibroblasts (CAFs) also contribute significantly to tumour angiogenesis. CAFs are of multiple origins: they can originate from resident fibroblasts, mesenchymal stem cells or mutated fibroblasts [84]. CAFs are able to produce cytokines and chemokines favouring inflammatory cells infiltration and consequently promoting angiogenesis and metastasis. SDF-1 producing CAFs play a key role in the recruitment of endothelial cells to the tumour site [85, 86]. CAFs are also able to produce CXCL14, this in turn enhances interactions with tumour cells and favour macrophage infiltration and M2 subset polarization [87]. Recent studies have shown that CAFs associated to incipient neoplasia exhibit a pro-inflammatory signature, characterized by an over-expression of SDF-1, IL-6 and IL-1 $\beta$  that lead to the recruitment of pro-angiogenic macrophages and sustain tumour growth [87]. In addition, CAFs also secrete FGF which is a well characterized pro-angiogenic growth factor [88].

## 4.9 Anti-angiogenic Cancer Therapy

It is currently accepted that the main pro-angiogenic factor secreted within the tumour mass is VEGF. For this reason several anti-angiogenic drugs have been developed to target VEGF or its receptor, VEGFR-2. A variety of drugs, such as antibodies against VEGF or its receptor, engineered proteins that mimic VEGFRs and small molecule receptor tyrosine kinase inhibitors that preferentially target VEGFR-2 (VEGFR-2/

flk-1/KDR) with high affinity effectively prevent the growth of many mouse tumours and tumour xenografts [31, 89–93]. Unfortunately, however, the striking benefits of anti-VEGF/VEGFR therapy observed in treating mouse tumours have not been translated to the clinic. These drugs have had only modest effects on human cancers.

## 4.10 Anti-angiogenic Chemotherapeutics

Currently there are several Food and Drug Administration (FDA) approved anti-angiogenic chemotherapeutic drugs, including bevacizumab (Avastin; Genentech), aflibercept, axitinib, imatinib, pazopanib, regorafenib, sorafenib, sunitinib, and vandetanib. The best characterized and most widely used anti-angiogenic chemotherapeutic agent is bevacizumab, a humanized antibody against VEGF. Like bevacizumab, aflibercept is an inhibitor of VEGF. Aflibercept is a recombinant fusion protein consisting of VEGF-binding domains for the extracellular moiety of human VEGF receptors 1 and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin; acting as a decoy VEGFR (VEGF trap) [94]. Axitinib, imatinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib are multi-targeted receptor tyrosine kinase inhibitors that inhibit pro-angiogenic receptors, such as VEGFRs, FGFRs and PDGFRs [94]. Although these anti-angiogenic chemotherapeutics either alone or in combination with other drugs have been shown to improve progression-free survival and overall survival in cancer patients, their efficacy is still distant from what was anticipated and is usually accompanied with serious side effects. In addition, variable results have been observed in the treatment of different types of cancers with these drugs, suggesting that the sensitivity and efficacy of anti-angiogenic therapy might be cancer specific [95].

## 4.11 Potential Pitfalls of Anti-angiogenic Therapy

A number of explanations have been put forward in order to explain the modest effectiveness of anti-VEGF/VEGFR therapy in cancer patients compared to laboratory mice. An obvious explanation is that cancer patients are often elderly and very ill, in contrast with the young, relatively healthy tumour-bearing laboratory mice. Furthermore, mice usually take much higher chemotherapeutic dosages compared to cancer patients, without taking into account toxic side effects. Another likely reason for the limited effectiveness of anti-VEGF/VEGR therapy is that it does not result in the killing of all tumour cells; as such the remaining cancer cells rendered hypoxic by a compromised blood supply are stimulated to produce and secrete increased amounts of VEGF that may overwhelm anti-VEGF/VEGFR therapy, especially when accompanied by increased expression of matrix components that

bind and sequester VEGF, protecting it from anti-VEGF drugs [96]. Hypoxic cancer cells also produce a plethora of other growth factors and cytokines, which have the capacity to stimulate new blood vessel formation and growth, including FGF, PDGF, HGF, EGF, IL-8, IL-6, Ang-2, SDF-1, PDGF-C, CXCL6, and others, as well as their receptors. The recruitment of vascular progenitor cells and pro-angiogenic immune cells (e.g. macrophages, mastocytes, NK cells, neutrophils) that can serve as a rich source of growth factors, cytokines and chemokines constitutes another possible mechanism for the lack of success observed with anti-VEGF/VEGFR cancer therapy [97, 98]. Several studies have also shown that VEGFR inhibitors are actually highly effective in preventing the development of the spontaneous Rip-Tag tumour and in inhibiting its early growth, but are much less beneficial in regressing tumours with an already established vasculature [97, 99]. Thus, in mice as in patients, anti-VEGF/VEGFR therapy was found to be less effective in advanced disease. Bergers and Hanahan attributed the failure of late therapy to the maturing of the vasculature with increased pericyte coverage and found that addition of a receptor tyrosine kinase inhibitor that targeted PDGFR- $\beta$  (highly expressed on pericytes) improved anti-VEGFR therapy [97]. Many other reports indicate that immature vessels are preferentially susceptible to anti-VEGF/VEGFR therapy [97, 99, 100]. There is microvascular heterogeneity within tumours, and not all activated endothelial cells express the same cell surface markers. Therefore, a pharmaceutical targeting a specific marker may not effectively inhibit tumour progression.

It is becoming increasingly clear that in order to develop highly efficient anti-angiogenic therapies, we probably need to target several pro-angiogenic key molecules simultaneously to effectively hinder tumour vascularization. Also, combinational therapies involving anti-angiogenic drugs directed at inhibiting vessel formation in conjunction with chemotherapeutics that specifically target/kill cancer cells have shown promising results [94, 95].

Once tumour angiogenesis is established the high density of blood vessels within the tumour site provides not only oxygen and nutrients that allow the tumour to grow, but also an escape route for the cancer cells (metastasis), for these reasons tumour angiogenesis is closely linked to poorer clinical outcome for cancer patients [2].

Angiogenesis constitutes the first/initial step of the tumour invasion/metastatic cascade, simultaneously with local invasion of connective tissue (to which endothelial cells contribute significantly, especially at the initial stages of tumour development); the next step of the invasion/metastatic cascade is intravasation, where cancer cells enter the blood vessels; followed by transport of the cancer cells in the blood stream; extravasation is then complied by the adhesion of cancer cells to the blood vessel and entry into tissues/organs in a distinct location from the primary tumour; formation of micrometastasis follows, which is the establishment of the cancer cells in these new tissues/organs and finally colonization comprises the proliferation of the newly established cancer cells in order to form large masses, macrometastasis.

### Multiple Choice Questions

1. Which cells provide structural stability, capacity to resist the blood pressure and impermeability to the blood vessels?

- (A) endothelial cells and pericytes
- (B) epithelial cells and pericytes
- (C) pericytes
- (D) endothelial cells
- (E) endothelial cells and smooth muscle cells

During arteriogenesis the endothelial cell channels become covered by pericytes, which provide structure and regulate blood vessel perfusion.

2. What is the main cellular receptor involved in the activation of proliferative and survival signaling in endothelial cells?

- (A) PDGF
- (B) PDGFR
- (C) VEGF
- (D) VEGFR
- (E) c-MET

VEGF binding to the VEGF receptor (VEGFR) at the surface of endothelial cells, stimulates endothelial cell proliferation, survival, secretion of matrix degradation enzymes (e.g. matrix metalloproteases and plasmin) and migration to the tumour site.

3. Which subunit(s) of HIF (Hypoxia Inducible Factor) is/are regulated by oxygen levels?

- (A) HIF- $\alpha$
- (B) HIF- $\beta$
- (C) HIF- $\gamma$
- (D) HIF- $\alpha$  e HIF- $\beta$
- (E) ARNT

The HIF-1 $\beta$  subunit is constitutively expressed in cells, while HIF- $\alpha$  is rapidly degraded in oxygenated cells. For this reason, HIF transcriptional activity is highly regulated through the stabilization of the HIF- $\alpha$  subunit. In the presence of oxygen, the enzymes prolyl hydroxylases (PHD) add hydroxyl groups to two proline residues of HIF- $\alpha$ . This modification allows binding of the ubiquitin ligase protein, Von Hindel Lindau (VHL), to HIF- $\alpha$  and the subsequent ubiquitination and degradation of HIF- $\alpha$  via the proteasome.

4. Which of the following proteins are secreted by cancer cells to promote extracellular matrix degradation?

- (A) interleukins
- (B) growth factors

- (C) matrix metalloproteases
- (D) cadherins
- (E) catenins

Cancer cells secrete proteolytic enzymes such as plasmin, urokinase-type plasminogen activator (uPA) (activator of the protease plasmin), and matrix metalloproteases, whose combined action induces degradation of the basement membrane and ECM components, release of sequestered growth factors from the ECM, destabilization of the vasculature as well as migration and proliferation of endothelial cells contributing significantly in this way to tumour angiogenesis.

5. Name the main reason why the blood vessels formed during tumoral angiogenesis are permeable.
- (A) Deficient recruitment of endothelial cells
  - (B) Excessive recruitment of pericytes
  - (C) Deficient recruitment of pericytes
  - (D) Deficient recruitment of epithelial cells
  - (E) Excessive recruitment of epithelial cells

Tumour angiogenesis is very different from normal angiogenesis in the sense that there is an excess of pro-angiogenic signalling that stimulate endothelial cell proliferation and migration, which is not accompanied by signals that lead to the recruitment and proliferation of pericytes and smooth muscle cells.

6. How do cancer cells inhibit the anti-angiogenic system?
- (A) Inactivation of Ras and activation of p53 lead to inhibition of Tsp-1
  - (B) Activation of Ras and inactivation of p53 lead to inhibition of Tsp-1
  - (C) Inactivation of Ras and activation of p53 lead to inhibition of VEGF
  - (D) Activation of Ras and inactivation of p53 lead to inhibition of VEGF
  - (E) Activation of Ras and p53 lead to inhibition of VEGF

Angiogenesis inhibition in tumours is usually compromised since the transcription of the *THBS1* gene that encodes for Tsp-1 is commonly impaired. *THBS1* transcription is strongly induced by p53. Conversely, the loss of p53 function, observed in a large percentage of human tumours, leads to a substantial decrease in Tsp-1 protein expression within the tumour mass. Oncogenes such as Myc, Ras, Src and Jun function in the opposite way inhibiting the transcription of the *THBS1* gene. Since constitutive activation of these oncogenes is frequently observed in tumours, this results in the inhibition of Tsp-1 protein expression and consequently also contributes to the inhibition of anti-angiogenic mechanisms in cancer patients.

7. Which of the following growth factors is secreted by endothelial cells to recruit pericytes?
- (A) HGF
  - (B) PDGF-B
  - (C) VEGF
  - (D) EGF
  - (E) TGF- $\alpha$

For a blood vessel to be perfectly functional, it must become mature and stable. Endothelial cells return to their quiescent state, and signals such as platelet-derived growth factor B (PDGF-B), angiopoietin 1 (ANG-1), transforming growth factor- $\beta$  (TGF- $\beta$ ), ephrin-B2 and NOTCH induce the coverage of the newly formed blood vessel with pericytes.

8. Which embryonic layer(s) give(s) rise to the epithelia lining the airways?
- (A) Ectoderm
  - (B) Ectoderm and endoderm
  - (C) Endoderm
  - (D) Mesoderm and ectoderm
  - (E) Mesoderm and endoderm

Epithelial cells derive from all three major embryonic layers. The epithelia lining the skin, parts of the mouth and nose, and the anus develop from the ectoderm; while cells lining the airways and most of the digestive system originate from the endoderm. The epithelium that lines vessels in the lymphatic and cardiovascular system derives from the mesoderm and is called endothelium.

9. How do prolyl hydroxylases (PHD) regulate HIF?
- (A) PHD add hydroxyl groups to two asparagine residues of HIF- $\alpha$  leading to its degradation via the proteasome
  - (B) PHD add hydroxyl groups to two proline residues of HIF- $\alpha$  leading to its degradation via the proteasome
  - (C) PHD add hydroxyl groups to two asparagine residues of HIF- $\alpha$  leading to transcriptional inhibition of HIF related genes
  - (D) PHD add hydroxyl groups to two proline residues of HIF- $\beta$  leading to its degradation via the proteasome
  - (E) PHD add hydroxyl groups to two proline residues of HIF- $\beta$  leading to transcriptional inhibition of HIF related genes

The enzymes prolyl hydroxylases (PHD) add hydroxyl groups to two proline residues of HIF- $\alpha$ . This modification allows binding of the ubiquitin ligase protein, Von Hindel Lindau (VHL), to HIF- $\alpha$  and the subsequent ubiquitination and degradation of HIF- $\alpha$  via the proteasome.

10. What are the advantages of the glycolytic metabolism for cancer cells?
- (A) More efficient in producing energy compared to aerobic respiration
  - (B) Oxygen dependent metabolism
  - (C) Production of metabolic intermediates that can be used in biosynthesis pathways
  - (D) Production of metabolic intermediates that can be used in catabolic pathways
  - (E) Production of metabolites for the TCA cycle

Even though glycolysis is not nearly as efficient as aerobic respiration regarding energy production, it does provide other advantages to the cancer cell. The glycolytic intermediaries can be readily used for the biosynthesis of DNA, RNA, lipid and aminoacids/ proteins which are critical processes in fast proliferating cells such as cancer cells. In addition the glycolytic metabolism renders cancer cells independent of oxygen availability within the tumour mass, which can be very variable with the progression of the tumour.

11. Which of the following VEGF family members have a relatively minor role in the regulation of angiogenesis?
- (A) PlGF and VEGF-B
  - (B) VEGF-A and VEGF-C
  - (C) PlGF and VEGF-C
  - (D) VEGF-B and VEGF-C
  - (E) VEGF-C AND VEGF-D

VEGF is the main component of this family, and it stimulates angiogenesis both in physiological and pathological processes. In contrast to VEGF, PlGF and VEGF-B appear to have a relatively minor role in the regulation of angiogenesis, but have been shown to play a role in cardiac muscle function.

12. Which protein(s) induce the migration of endothelial cells to the provisional extracellular matrix scaffolding during angiogenesis?
- (A) EGF
  - (B) Matrix metalloproteases
  - (C) Plasmin
  - (D) Interleukins
  - (E) Integrins

During angiogenesis VEGF increases the permeability of the endothelial cell layer, causing plasma proteins to extravasate from the vessel and to lay down a provisional ECM scaffold. In response to integrin signalling, endothelial cells migrate onto this ECM surface.

13. Which of the following processes is not induced by tumor hypoxia?

- (A) angiogenesis
- (B) cellular proliferation
- (C) epithelial to mesenchymal transition
- (D) mesenchymal to epithelial transition
- (E) invasion

HIF is the main regulator of the cellular response to hypoxia, inducing the transcription of over one hundred genes involved in critical processes, such as angiogenesis, alteration of cellular metabolism, cellular pH regulation, cell survival, migration, invasion, epithelial to mesenchymal transition and cell proliferation.

14. How do tip cells sense environmental guidance cues such as ephrins and semaphorins?

- (A) They rely on stalk cells
- (B) They have filopodia
- (C) They secrete matrix metalloproteases
- (D) They over-express EGF
- (E) They over-express integrins

To build a perfused tube and prevent endothelial cells from moving all together in a deregulated fashion towards the angiogenic signal, one endothelial cell, named the tip cell, becomes selected to lead the tip in the presence of factors such as VEGF receptors, neuropilins and the NOTCH ligands, DLL4 and JAGGED1. Tip cells have filopodia to sense environmental guidance cues such as ephrins and semaphorins.

15. The anti-angiogenic protein, angiostatin is a degradation product of which protein?

- (A) Matrix metalloprotease 2
- (B) Matrix metalloprotease 9
- (C) Plasminogen
- (D) VEGF
- (E) PlGF

Angiostatin is a degradation product of plasminogen (Plg), constituted by kringle 1–3 of Plg. Angiostatin binds to proteins expressed on the surface of endothelial cells, such as annexin A2 heterotetramer (AII<sub>t</sub>), angiomin, integrin  $\alpha\beta 3$ , c-met and ATP synthase functioning as a negative regulator of these proteins and consequently inhibiting angiogenesis.

16. Which of the following proteins is not secreted by tumor associated macrophages in order to induce tumor angiogenesis?

- (A) endostatin
- (B) matrix metalloproteases
- (C) CXC chemokines



- (D) TGF- $\beta$
- (E) TNF- $\alpha$

TAMs secrete a wide range of pro-angiogenic mediators, the most important of which being VEGF, but also including epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), PDGF, thymidine phosphorylase (TP), angiopoietin receptor Tie2, angiogenic CXC chemokines (CXCL8/IL-8 and CXCL12, also known as stromal derived factor-1, SDF-1), transforming growth factor beta (TGF- $\beta$ ), tumour necrosis factor alpha (TNF- $\alpha$ ), adrenomedullin (ADM), uPA and metalloproteases, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12.

17. Which chemokine is secreted by cancer cells to recruit neutrophils?

- (A) CXCL12
- (B) CCL2
- (C) CCL5
- (D) CXCL10
- (E) CXCL8

CXCL8, which is abundantly produced by tumour cells, represents a potent chemoattractant for the recruitment of neutrophils to the tumour mass. CXCL8 is also associated with angiogenesis by directly activating the CXCR2 receptor on endothelial cells.

18. The anti-angiogenic chemotherapeutic bevacizumab is:

- (A) dominant-negative VEGF protein
- (B) antibody against VEGF
- (C) inactive ligand for VEGFR2
- (D) antibody against VEGFR2
- (E) cross linker for VEGFR2

The best characterized and most widely used anti-angiogenic chemotherapeutic agent is bevacizumab, a humanized antibody against VEGF.

**Answers:**

1. (C) pericytes
2. (D) VEGFR
3. (A) HIF- $\alpha$
4. (C) matrix metalloproteases
5. (C) Deficient recruitment of pericytes
6. (B) Activation of Ras and inactivation of p53 lead to inhibition of Tsp-1
7. (B) PDGF-B
8. (C) Endoderm
9. (B) PHD add hydroxyl groups to two proline residues of HIF- $\alpha$  leading to its degradation via the proteasome
10. (C) Production of metabolic intermediates that can be used in biosynthesis pathways

11. (A) PlGF and VEGF-B
12. (E) Integrins
13. (D) mesenchymal to epithelial transition
14. (B) They have filopodia
15. (C) Plasminogen
16. (A) endostatin
17. (E) CXCL8
18. (B) antibody against VEGF

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# Chapter 5

## Genetic Basis of Metastasis



Catherine A. Moroski-Erkul, Esin Demir, Esra Gunduz, and Mehmet Gunduz

**Abstract** The variation between and among the many types of cancer presents a formidable challenge both to practicing clinicians and medical researchers. There are several characteristics that are common to all cancers such as unrestrained proliferation and evasion of cell death. Another common feature is that of metastasis. Metastasis is “initiated” when primary tumor cells acquire the ability to invade surrounding tissues and eventually develop secondary tumors in distant locations. This process appears to rely not only on changes at the genetic level of tumor cells themselves but also from their interaction with surrounding stromal cells and the immune system. The genetic and molecular changes that give rise to metastatic change are of special interest due to the significant decline in a patient’s prognosis after metastasis has occurred. A host of genes and pathways involved in several pathways have been implicated in this process, several of which will be reviewed in detail.

**Keywords** Genetics · Cancer · Metastasis · EMT

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## 5.1 Introduction

Our understanding of the processes of tumorigenesis and metastasis has evolved over time. During the last decade the use of automated high-throughput screening methods has become more widespread and the costs of DNA sequencing and microarray analysis have significantly declined. Large-scale studies have allowed scientists to identify genes and signalling pathways that contribute to a tumor cell's capacity for metastasis. Perhaps the most important contribution to our understanding of metastasis has been a move away from reductionist approaches to the study of this disease process. The development of new *in vivo* models has significantly aided in our understanding of metastasis, a process that is likely impossible to mimic *in vitro*. For example, in the Rip-Tag transgenic mouse model of pancreatic islet cell tumorigenesis, forced expression of VEGF-C in tumor islet cells encourages metastasis via lymph nodes [62]. Also, improvements in *in vivo* live imaging techniques have the potential to provide major breakthroughs in our understanding of cancer metastasis [9, 17].

Metastasis occurs when cells from a primary tumor acquire the capacity to travel to other parts of the body and form secondary tumors. It is a complex and spectacularly inefficient process. Cancer cells escape from the primary tumor each day but only a tiny fraction of these survive. Of those that manage to survive challenges present in the general circulation, such as hydrodynamic shear forces and immune cells, even fewer will go on to colonize other parts of the body, and yet fewer still are able to successfully form metastatic lesions [11, 40]. Cells capable of metastasis may not go on to form detectable metastatic lesions immediately upon colonization of another part of the body [50]. For reasons not yet clear, not all types of cancer are equal in terms of capacity to metastasize. Cancer of epithelial tissue are far more likely to become life-threatening via metastasis than cancers originating from other tissues. Metastasis is a dreaded diagnosis as it carries a very poor patient prognosis (American Cancer Society (2011). Cancer Facts and Figures 2011. Atlanta, GA: American Cancer Society). Metastasis is the cause of death in 90% of deaths from solid tumors [62].

Although the characteristics of metastasis typically vary by cancer type, there are some general trends that have been identified from large-scale analysis of patient data. Tumor size and regional lymph node involvement are among the two most important predictors of future [14]. Although tumor size being predictive of prognosis is at first glance logical, in that a larger mass of cells is mathematically more likely to have acquired genetic changes that may contribute to metastatic ability, this is not always the case. Some patients present with metastatic disease with an unidentifiable primary tumor (cancer of unknown primary or CUP). As for the predictive ability of nodal involvement, in the case of sarcomas, nodal involvement is seen in less than 3% of patients [18]. Tumor grade, depth of invasion and lymphovascular invasion are also important predictors of metastatic risk across cancer types [10, 14]. Patterns of metastasis also differ by cancer type and can differ among individuals, however certain trends have been clearly identified. For example, in colon cancer, the most common site of metastasis is liver (via venous blood flow from the



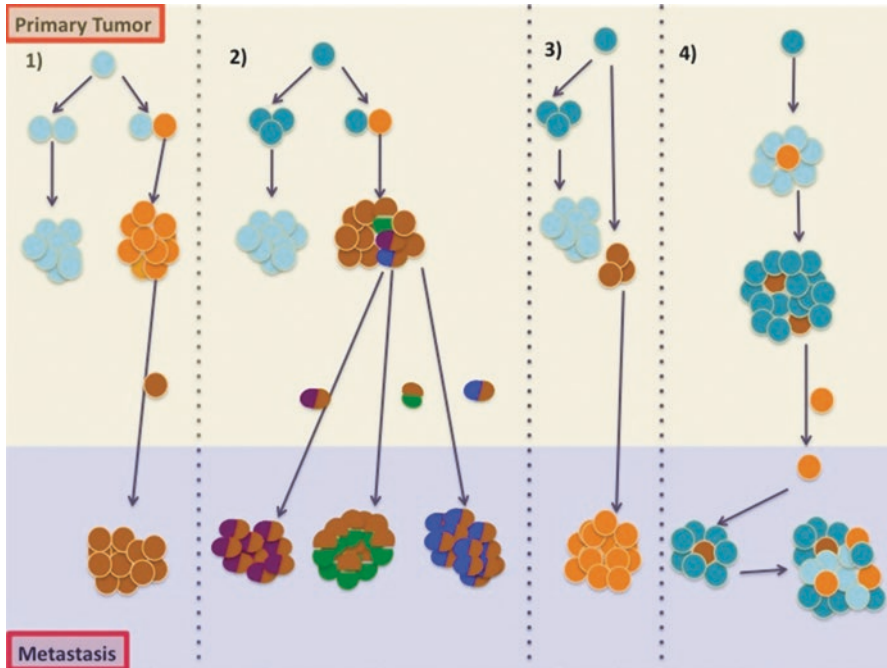
colon to the liver) and in breast cancer they are the contralateral breast tissue and lymph nodes (via lymphatic channels).

## 5.2 Models of Cancer Metastasis

Many different models of tumorigenesis and metastasis have been put forth over the years. Both the Halsted and later Fisher models of metastasis in breast cancer were limited in their ability to explain variations observed in clinical data. Hellman suggests that a more useful view is that of breast cancer as a complex spectrum of diseases which can be explained by both predetermination and traditional progression models [28]. In the clonal dominance model, cells with metastatic ability take over and dominate the overall population of the tumor [58]. The dynamic heterogeneity model posits that metastatic variants occur at a certain frequency within the tumor cell population and are unstable. Thus their turnover limits the overall capacity of a tumor to become metastatic [26]. The ability to determine patient prognosis by DNA microarray analysis of primary tumors suggests that cells with metastatic ability may not be as rare as suggested by some models of metastasis. Such data seems to point toward a model in which genetic changes acquired relatively early on in disease progression that are necessary for tumorigenesis are also necessary for metastasis (Fig. 5.1). This would help to explain cases of cancer of unknown primary. Yet again we are confronted with clinical data at odds with this explanation, such as the success of early screening in reducing cancer mortality. Also, cases in which cancer cells remain dormant for long periods of time after removal of primary tumors only to re-appear years later in distant sites suggest that additional mutations are necessary for successful metastasis. Yet global gene expression analysis of primary and metastatic tumors reveals, time and again, very little difference between the two expression patterns. This suggests that a very small number of key genes are required to tip the scales and make metastasis possible. Another hypothesis that is gaining ground is that cancer cells, either through changes in their immunogenic properties or damage to the host immune system, acquire the ability to evade destruction by immune surveillance.

As is typically the case with considering a spectrum of diseases as complex as cancer, it is likely that no single model will suffice to explain all of metastatic cancer. What can be said with relative certainty is that metastasis follows a basic set of progressive steps. The basic steps involved in metastasis (Fig. 5.2) are as follows:

1. Acquisition of the capacity to invade local tissues
2. Intravasation (gaining access to the circulation)
3. Extravasation (exiting from the circulation)
4. Formation of micrometastasis in a new environment and colonization (growth into macrometastasis)



**Fig. 5.1 Models of breast cancer metastasis**

Serving as a model of metastasis, there are several proposed pathways via which primary breast cancer tumors might metastasize. In the left-most model (1), tumor cells acquire the capacity to metastasize early in the process of tumorigenesis. Shown in the second model is the tendency for some tumors to produce different clones that each harbor different capacities for metastasis and tissue-specific metastatic proclivities. The next model (3) is a representation of the parallel evolution model. Here, metastatic tumor cells are dispersed from the primary tumor very early and develop separately from and in parallel with the primary tumor. The fourth model depicts the cancer stem cell model in which only stem cells have metastatic capacity. (Adapted from Ref. [60])

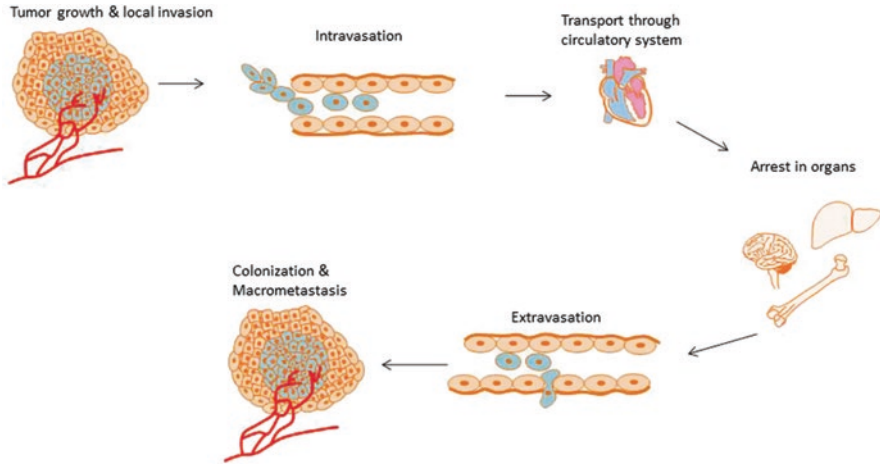
Each of these steps require the acquisition of a host of specialized characteristics/functions. This chapter will discuss some of the genetic changes that aid cancer cells in their acquisition of these characteristics.

## 5.3 Stages of the Metastatic Process

### 5.3.1 Signalling Pathways Involved in Local Invasion

#### 5.3.1.1 Epithelial to Mesenchymal Transition

More than 80% of cancers are carcinomas; that is they are of epithelial tissue origin. Carcinomas are complex masses of cells, of which as much as 90% can be non-neoplastic. This diverse collection of non-neoplastic cells compose the tumor



**Fig. 5.2 Stages of metastasis**

Cancer is generally thought to progress in a step-wise fashion. Tumor cells that acquire the necessary characteristics to “escape” from a primary lesion and locally invade surrounding tissue may then enter into the general circulation via intravasation. From here, tumor cells that survive the harsh environment (shear forces, lack of support structure, growth signals, etc.) can take up residence in distant tissues, again making their way through the endothelial barrier via extravasation. Tumor cells here form micrometastatic colonies that may or may not go on to form macrometastases

stroma. These cells are mostly of mesenchymal origin and are either remnants of the tissue that was invaded by the neoplastic cells or are “recruited” from the surrounding tissue by the neoplastic cells to aid in their growth and survival. Hodgkin’s lymphoma is an extreme example of this phenomenon. In this disease, 99% of the cells in a tumor are non-neoplastic and surround the rare neoplastic Reed-Sternberg cells.

As is the case in normal epithelial tissue, tumors of epithelial origin rely on heterotypic signalling (signalling between different cell types) between stromal cells and the neoplastic epithelial cells for maintenance of tumor growth and architecture. As the neoplastic epithelial cells proliferate, trophic signals are released and are in turn sensed by cells of the stroma which carry receptors specific for such signals. Thus the tumor and stroma cells proliferate concurrently. These stromal cells can even be found layered within metastases originating from these primary carcinomas, highlighting the interdependence between neoplastic and non-neoplastic cells in a tumor.

The process of epithelial to mesenchymal transition (EMT) involves an alteration in both morphology and gene expression pattern of epithelial cells to that of mesenchymal cells. It is necessary during wound healing to allow re-shaping of the epithelial cell layers and also for some morphogenetic processes of embryogenesis. These are known as type II and type I EMT, respectively [33]. Growing evidence suggests that this process is “hijacked” by cancer cells and used to significantly change their morphology and motility, thereby allowing them to invade nearby tissue. This process is known as type III EMT. It has also been suggested to play a role in cancer progression through maintenance of stem cell-like properties, prevention

of apoptosis and senescence, and suppression of immune responses [54]. This is triggered in part by *ras* oncogene activation within neoplastic tissue cells but also is contributed to by chemical signals from non-neoplastic cells outside the tumor proper.

The leading edges of carcinomas exhibit an EMT front where they are invading surrounding tissue. This can often be seen in immunostained tissue slices containing tumor and non-neoplastic tissue side-by-side. Cancer cells at the edge of the invading tumor do not express epithelial cell surface markers such as E-cadherin, a protein which is strongly expressed by cells in the center of tumors and allows epithelial cells to adhere to one another. Instead, cells express surface markers characteristic of fibroblasts such as vimentin, N-cadherin and fibronectin. Loss of E-cadherin expression through epigenetic silencing or expression of mutant forms of this protein has been identified in many carcinoma types and is possibly the single most important change contributing to this type of tumor's ability to become locally invasive. Several signaling pathways (WNT, TGF- $\beta$ , FGF, EGF, STAT3 and NF- $\kappa$ B) suppress E-cadherin expression via the transcriptional repressors SNAIL, SLUG and TWIST [14, 56]. The expression of E-cadherin and its associated catenins can also be down-regulated via growth factor mediated-phosphorylation and subsequent proteosomal degradation. These growth factors include epidermal growth factor receptor (EGFR) [27], c-MET (hepatocyte growth factor receptor or HGFR) [31], fibroblast growth factor receptors (FGFRs) [15], Src-family kinases and insulin-like growth factor 1R (IGF-1R) [14]. The degradation of E-cadherin leads to nuclear translocation of  $\beta$ -catenin which affects transcription of genes including the oncogene *c-myc* and the cell cycle regulator cyclin D1 [56]. The expression of N-cadherin by tumor cells allows them to move into the stroma of the epithelial tissue where other N-cadherin expressing fibroblasts reside. Like E-cadherin, N-cadherin expressing cells bind to one another, however with much less strength than the bonds formed by E-cadherin.

Once these tumor cells escape from the tissue of origin and take up residence in another part of the body, they may find themselves in an environment with a different set of extracellular signals. This may result in a reversion back to the epithelial phenotype, thus becoming more like the cells in the center of the primary tumor from which they originated. This mimics the mesenchymal to epithelial transition or MET, which is, like EMT, also involved in wound healing and embryogenesis and may explain why distant metastases often resemble the primary tumors from which they originated. This conversion would also allow cells to regain epithelial cell-cell adhesion and facilitate colonization at new sites [56].

Two other cell transition processes have been described and involve an amoeboid cell phenotype: the collective to amoeboid transition (CAT) and the mesenchymal to amoeboid transition (MAT). CAT is caused by  $\beta$ 1-integrin inhibition. MAT is triggered by inhibition of proteases and relies on signalling via Rac, Rho/ROCK and EphA2. Amoeboid cancer cells differ significantly from mesenchymal cancer cells. As a result of their unique transition they completely lose cell polarity, are capable of chemotaxis and have very loose attachments to extracellular matrix [56]. They also migrate significantly faster than mesenchymal cancer cells with a speed of up to 20  $\mu$ m/min versus 0.1–1  $\mu$ m/min [20]. They do so by mechanically disrupting

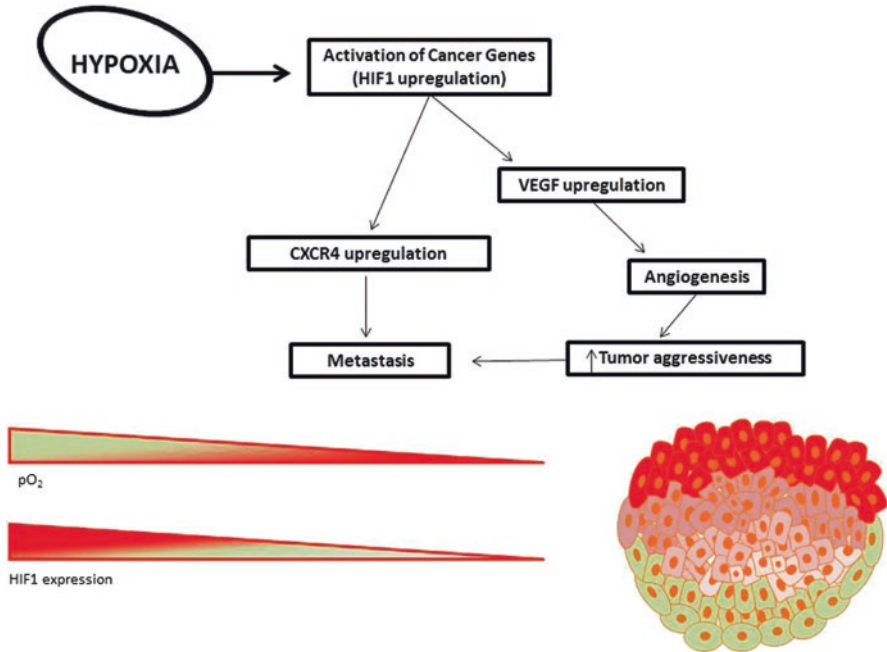
matrix structures rather than using proteases to degrade them [21]. Ameoboid cancer cells usually are seen after a patient has been treated with integrin or protease inhibitors. Matrix metalloproteinase (MMP) inhibitors appear to have little to no effect on inhibition of cancer progression in such cases [22, 49].

Transmission of signals between the tissue stroma and tumor is achieved largely via transforming growth factor beta (TGF- $\beta$ ) along with tumor necrosis factor alpha (TNF- $\alpha$ ), insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF) and hepatocyte growth factor (HGF). Interaction between TGF- $\beta$  and *ras* oncogenes may trigger EMT. Raf, which is immediately downstream of Ras, can also trigger EMT. Phosphoinositide 3-kinase (PI3K) in turn protects cells from pro-apoptotic functions of TGF- $\beta$  [62]. TNF- $\alpha$ , produced by inflammatory cells in the early stages of tumor progression, together with TGF- $\beta$ , are important not only for the initiation but also the maintenance of EMT, via maintenance of NF- $\kappa$ B signalling. NF- $\kappa$ B is a key transcriptional regulator of the inflammatory response and is widely activated in cancer.

In the case of non-epithelial tumors, such as those of hematopoietic and connective tissue and the central nervous system (CNS), the waters are quite muddy. It is possible that an EMT-associated transcription factors are important in the case of CNS, as it is derived from an early embryonic epithelium [61].

### 5.3.1.2 Hypoxia and an Activated HIF Program

Hypoxia inducible factor-1 (HIF1) is an oxygen sensitive transcriptional activator and as such is a key regulator for induction of genes that facilitate adaptation and survival of cells from normoxia (~21% oxygen) to hypoxia (~1% oxygen). It is composed of two subunits, alpha and beta. The beta subunit is constitutively expressed and the alpha subunit is responsive to oxygen. It is key in the adaptation of cancer cells to hypoxia through its activation of a set of genes that are involved in angiogenesis, iron and glucose metabolism, and cell proliferation/survival (Fig. 5.3). Angiogenesis-associated genes such as vascular endothelial growth factor (VEGF), prostaglandin derived growth factor (PDGF) and angiopoietin-2 are upregulated by HIF-1 $\alpha$ . Also upregulated are matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2) and C-X-C chemokine receptor type 4 (CXCR4). While these genes are involved in tumorigenesis, they also serve functions specific to metastasis. MMP-1 helps dissolve the basement membrane and MMP-2 alters architecture of the extracellular matrix. Dissolution of the basement membrane is a key step in migration as it gives tumor cells access to blood and lymphatic vessels in the stroma. CXCR4 in turn causes cancer cells to migrate towards areas of angiogenesis [14]. Inactivation of the p53 signalling system, which would normally activate cell death in conditions of low oxygen, contributes to the ability of cancer cells to survive in a hypoxic environment. Evasion of cell death and the ability to revert to glycolysis for cellular respiration are essential for survival once tumor cells have entered the circulation. Thus characteristics that provide a selective advantage to some cells during tumorigenesis also come in handy once cells exit into the circulation.



**Fig. 5.3 Hypoxia in cancer**

Due to rapid proliferation, tumors suffer from a lack of sufficient oxygenation. Cells deeper within the tumor (red and pink cells) have less access to oxygen than those found in the perimeter (green cells). As the partial pressure of oxygen ( $pO_2$ ) drops, HIF1 expression increases. Hypoxia leads to upregulation of many genes involved in metastasis, including CXCR4 and VEGF. CXCR4 expression causes cells to migrate toward areas of angiogenesis and may lead to chemokine-mediated organ-specific metastasis. VEGF upregulation leads to angiogenesis which increases tumor aggressiveness as well as the tumor's capacity for metastasis

HIF-1 $\alpha$  expression and tumor hypoxia are both prognostic markers of patient outcome and metastasis in several cancer types [30, 41, 55].

### 5.3.1.3 Intravasation

The processes of intra- and extravasation are not as well understood as invasion. What is known for certain is that tumor cells encounter unique challenges upon entering the circulation. Most cells require attachment to some kind of substrate for survival and in the absence of such substrate, cells can undergo a form of apoptosis known as anoikis. These circulating cells must also be capable of surviving in the absence of the mitogenic and trophic factors that were present in the stroma from which they originated. Shear forces within vessels can simply tear cells apart. Those that manage to reach larger vessels, some of which may do so by associating with an entourage of platelets, will eventually pass through the heart, after which they

will most likely become lodged within the capillaries of the lungs. However, not all metastasis occurs in lungs and thus these cells somehow manage to pass to larger passageways and travel to distant locations in the body. This is likely achieved through arterial-venous shunts. Cells may also pinch off large portions of their cytoplasm and the remaining cell size may be small enough for them to maneuver through the small capillaries. At some point, the cells will need to exit the circulation in some way or another, a process known as extravasation.

#### 5.3.1.4 Extravasation

In extravasation, we encounter yet another instance of cancer cells hijacking an already existing process for their benefit. Circulating tumor cells express selectin ligands, a group of transmembrane glycoproteins that are also expressed on leukocytes. These proteins are essential for leukocyte transmigration from the circulation to sites of tissue damage or infection, an important component of the body's adaptive and innate immune response. Selectins expressed on cells that line the vascular walls bind to selectin ligands on leukocytes and cancer cells. This binding is relatively weak and, combined with shear forces in the circulation, results in a sort of rolling movement along the vessels. At some point, a cell or group of cells may become lodged in the vessel. Cells may then proliferate, creating a small tumor that eventually bursts through the vessel wall. Expression of VEGF by cancer cells can also facilitate their extravasation via enhancing endothelial permeability and disrupting the junctions between endothelial cells. Cancer cells with an amoeboid phenotype can easily squeeze through junctions that cells normally would be prevented from traversing. Expression of CXCR4 by cancer cells may result in the selective extravasation of into organs that express CXCL12, such as liver, lung, bone and lymph nodes. Expression of CXCR4 on tumor cells leads to selective extravasation into organs that constitutively express CXCL12 such as liver, lung, bone and lymph nodes [44, 65].

In breast cancer, a gene signature associated with lung metastasis has been identified. Four of the genes in this signature (EGFR, MMP1, MMP2 and COX2) have been shown to facilitate blood vessel growth and appear to be essential for extravasation into the lung. Inhibition of these genes resulted in the entrapment of cancer cells within vessels [14, 42]. Again we also see the action of *Twist*, in this case increasing the ability of cancer cells to migrate intravascularly and extravasate [17, 34, 53].

#### 5.3.1.5 Colonization & Macrometastasis

After successful extravasation, cells must have the ability to colonize (that is, survive and proliferate) in the new tissue. Antibodies against cytokeratins are used to detect micrometastases in primary carcinoma while epithelial cell adhesion molecule (EpCAM) antibodies can be used to detect micrometastases in lymph nodes. Most extravasated cancer cells do not actually go on to form macrometastases and

it can take decades for tumor cells to form clinically detectable metastases after primary tumors are removed [14]. This is referred to as dormancy [1].

The processes involved in this are not well understood. The dormancy period may reflect entry into a state of senescence or may result from active immune surveillance that is able to rid the body of most, but not all, of the cells within micrometastases.

### 5.3.2 *Evading the Immune System*

The body has a number of mechanisms that it uses to ward off cancer development. At the cellular level there is the pRb circuit, DNA repair mechanisms and the apoptotic machinery. At the tissue level, cells that detach from the basement membrane typically undergo anoikis. Until about a decade ago, the role of the immune system in cancer was a highly debated one but evidence of its capacity to identify and destroy cancer cells has been steadily accumulating. First, a body of work in mice provided strong indications for an important role of the immune system in defense against cancer. The development of technology to genetically engineer mice led to the creation of mouse strains deficient in genes that play specific roles in the immune system, such as IFN- $\gamma$ , perforin, Rag1 and Rag2. These knock-out mice provided key advancements in our understanding of the relationship between the immune system and the development of cancer. But what about humans?

It has been observed that people with compromised immune systems are more likely to develop certain kinds of cancer. Organ transplant recipients, who receive long-term immunosuppressive therapy to prevent rejection of the transplanted tissue, have a very high increased risk of developing some kind of cancer. Cancers of viral origin occur at a much higher frequency in those who are immunocompromised. Kaposi's sarcoma (caused by human herpes virus 8) occurs in HIV patients at a rate 3000 times higher than in the general population and tumors caused by human papilloma virus are far more frequent in organ transplant recipients and AIDS patients [61].

The immune system may also be able to recognize tumors of nonviral origin, but it is not clear whether this is indeed the case. Anti-tumor antibodies have also been detected in the blood of cancer patients but it is not known whether these antibodies function in the removal of cancer cells from the body. Another example are tumor-infiltrating lymphocytes which may be recruited to the tumor to aid in its growth *or* may have invaded the tumor upon recognizing it as "foreign". The presence of these lymphocytes in several tumor types correlates with improved survival but there is no direct evidence that these are the cause of said improved survival.

The immune system can actively attack circulating tumor cells. For example, natural killer (NK) cells can engage cancer cells via TNF-related molecules such as TRAIL or CD95L, or through the perforin pathway. Both cause tumor cell death, and inhibiting TRAIL or using mice that are deficient in NK cells leads to increased metastasis [14].



### 5.3.3 *The Role of Cancer Stem Cells in Metastasis*

The concept of cancer stem cells (CSCs), first developed over a decade ago, was at first a controversial hypothesis. Accumulated evidence now strongly supports the existence of such cells in a variety of cancers including several leukemias and many solid tumors [3]. The genetic characteristics of CSCs vary by cancer type and even subtype. However, they share in common a high tumorigenic and metastatic potential with unlimited self-renewal capacity. They appear to be resistant to conventional therapies and often able to enter quiescence and/or a state of slow-cycling. This characteristic may explain, at least in part, the dormancy observed in patients whose cancer re-appears decades after initial therapy [1]. It could also explain why CSCs are not as sensitive as other cancer cells to cytotoxic drugs that target actively cycling cells.

This tumor sub-population was named for their similarity to normal adult stem cells present in tissues such as the gastrointestinal mucosa and cells of the hematopoietic system. Due to genetic and epigenetic instability, the CSC population within a single primary tumor is heterogeneous. CSCs are not necessarily the “cell of origin” that first gave rise to the primary tumor as cells within the tumor population may undergo changes over time that confer their “stemness”. Another characteristic of CSCs is that they tend to have high expression of EMT markers. Aktas et al. showed that, in patients with metastatic breast cancer, non-responders to treatment had significantly higher expression of EMT markers (62% vs 10% in responders) and ALDH1 (44% vs 5% in responders) [2].

The resistance that CSCs exhibit to conventional drugs may be caused by increased capacity for drug efflux, increased expression of free radical scavengers and increased DNA repair capacity [3]. A great deal of research is now focused on targeting the CSC niche as it appears to be essential for complete eradication of the disease. This has been achieved in part by gene expression profiling of CSCs to identify unique targets. An antibody therapy designed against a CSC-specific isoform of CD44 (CD44v6) resulted in severe skin toxicity in phase I trials for head and neck squamous cell carcinoma [48]. Other antibody therapies against markers such as CD123 and CD133 face challenges due to their also being expressed by normal stem cells. Such targets carry a high potential for toxic side-effects, much like traditional chemotherapeutic drugs.

Another method being developed is pre-treatment with a drug aimed at sensitizing the CSCs to conventional therapy. Francipane et al. reported sensitization of colon cancer to chemotherapy after treatment with IL-4 inhibitor [19]. Yet another means of overcoming the resistance of CSCs involves the inhibition of TGF pathway by bone morphogenetic proteins (BMPs). In a mouse xenograft model of brain cancer, this caused differentiation of the CSCs and subsequent cure [16]. Drug efflux pathways may also be targeted to sensitive CSCs to conventional chemotherapy.

### 5.3.4 *New Targets in the Clinic*

As our understanding of cancer has evolved so has the approach to treatment. Although classical chemotherapeutic drugs, radiotherapy and surgical resection are still the most common modes of treatment for most cancer types, there is a trend toward more targeted and individualized therapy. Here we discuss some of the recent developments in treatment specifically targeting metastasis.

Inhibitors of the CXCR4-CRCL12 chemokine axis are currently in Phase I and II clinical trials. This receptor-ligand pair is involved in cell migration during embryogenesis and wound healing. It has been implicated in cancer cell migration and its expression correlates with poor prognosis in colon, breast and gallbladder cancers [29, 46, 63, 64]. Organs and tissues that possess high levels of CRCL12, such as liver, lung, bone marrow, and lymph nodes, attract the migration of CXCR4-expressing cancer cells [13]. Upregulation of HIF1- $\alpha$ , which is involved in the adaptation of cancer cells to a hypoxic environment, also leads to increased gene expression of CXCR4 thus contributing to the progression of cancer [47]. CXCR4 expression is currently used as a biomarker of aggressive breast cancer and represents a potentially important target for therapy.

Combination therapy with CXCR4 antagonists, such as plerixafor, disrupts the interaction between CLL and stromal cells, recirculates CLL cells into the bloodstream and exposes them to conventional drugs [8]. This same drug was effective in minimizing the invasion and metastasis of epithelial ovarian cancer cells [4]. In combination therapy with decarbazine, plerixafor significantly suppressed the metastasis of melanoma as compared with decarbazine treatment alone [36]. Study of these molecules and the pathway in which they function should lead to better and more specific inhibitors. It should be noted that successful treatment may require combined inhibition of other protein targets in this pathway.

Another interesting tack under investigation is the targeting of epigenetic mechanisms. Epigenetic changes appear to occur early in the process of tumorigenesis [25]. During TGF- $\beta$  mediated EMT, there is a global reduction in the heterochromatin mark H3 Lys9 dimethylation (H3K9me2), an increase in the euchromatin mark H3 Lys4 trimethylation (H3K4me3) and an increase in the transcriptional mark H3 Lys36 trimethylation (H3K36me3) [59].

Epigenetic agents in the clinic include DNA demethylating drugs and histone deacetylase/demethylase inhibitors. The aim of treatment with DNA demethylating agents is to re-activate the expression of key regulatory genes that are silenced during cancer progression via methylation of CpG islands. The first DNA methylation inhibitor to be used in the clinic was 5-azacytidine, synthesized nearly 50 years ago and used to treat acute myelogenous leukemia [12]. It is now also approved for the treatment of myeloid dysplastic syndrome and chronic myelomonocytic leukemia. Its relative, 5-aza-2'-deoxycytidine, is approved for myeloid dysplastic syndrome and acute myelogenous leukemia. The main concern with these drugs is their high level of systemic toxicity and thus there is ongoing work to identify more specific inhibitors. Gemcitabine, an analogue of pyrimidine cytosine, is structurally similar

to 5-aza-2'-deoxycytidine and appears to reactivate several epigenetically silenced genes via destabilization and inhibition of DNA methyltransferase 1. It is used as monotherapy or in combination with cisplatin for the treatment of several solid tumors [24, 57]. RNAi techniques have shown that more specific inhibition of DNA methyltransferases may also be effective. However, these methods have not yet been tested *in vivo* so it remains to be seen whether these results will hold up at the organismal level [25].

Histone deacetylase inhibitors (HDACi), long used in treatment of some psychiatric disorders and as anti-epileptics, have caught the attention of researchers in other fields including those studying cancer, inflammatory and parasitic diseases [6]. HDACs affect many different physiological processes. Their inhibition in cancer cells leads to cell cycle arrest, apoptosis, autophagy and anti-angiogenesis. Their specificity toward malignant cells is of particular interest. Two drugs have been approved by the U.S. FDA for treatment of progressive, persistent or recurrent cutaneous T-cell lymphoma (Vorinostat, approved in 2006; and Romidepsin, approved in 2009) [35]. There are currently about a dozen small molecule inhibitors in ongoing clinical trials for several blood cancers, as well as lung, ovarian, and breast cancers and hepatocellular carcinoma [51]. It should be noted that the autophagy triggered by HDACi may be a mechanism of resistance rather than cell death [35].

Another target of increasing interest is the TGF- $\beta$  pathway, in part because it is involved in so many aspects of cancer development and progression [39, 45, 54]. However, approaches to this pathway must be considered carefully as it plays a dual role in cancer, as both tumor suppressor and tumor promoter [52]. There is a wide range of approaches being taken to inhibit TGF- $\beta$ , including antisense molecules, monoclonal antibodies and TGF- $\beta$  receptor kinase inhibitors (current small molecules in pre-clinical and clinical trials are reviewed in Sheen et al. [52]).

Other targets of interest are cell adhesion molecules such as selectins and cadherins. Antagonists such as neutralizing monoclonal antibodies, competitive ligand inhibitors and metabolic carbohydrate mimetics have been designed to target cellular interactions with selectins [5, 37]. Selectins not only are important for the motility of cancer cells in vessels but also allow cancer cells to attach to platelets, resulting in platelet aggregation and the formation of blood clotting. Experimental models have shown a role for the coagulation pathway in metastasis and some clinical studies indicate that patients treated with anti-coagulants such as low molecular weight heparins (LMWH) tend to have better outcome, but the data is far from conclusive [32] (see Mandala et al. for anti-coagulant indications) [38]. The precise mechanism(s) involved are unclear but may be associated with platelet-covered cancer cells being able to evade immune surveillance and lysis by natural killer cells [23]. Inhibition of P-selectin and heparanase by semi-synthetic sulfated hexasaccharides were shown to inhibit metastasis in mouse xenograft models using colon carcinoma cells (MC-38GFP) and a melanoma cell line (B16-BL6). The inhibition was similar to that seen in mice deficient in P-selectin [7].

There is currently a clinical trial underway for patients with previously untreated multiple myeloma ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT01518465) that includes an anti-coagulant, dalteparin (an LMWH), which inhibits P-selectin and L-selectin

binding to cancer cells [43]. Mousa Petersen Previous studies including dalteparin suggest that it is not useful in treating metastatic disease but may be helpful in patients with better prognosis [32]. Thus, P-selectin inhibition may prove to be useful in the prevention of metastasis, while patients already suffering metastatic disease may not benefit from such treatment. However, studies with new-generation P-selectin specific inhibitors are likely necessary before a conclusion can be drawn on this matter. SelG1 is an anti-P-selectin monoclonal antibody currently in Phase II clinical trials for pain management in sickle cell disease. Inclacumab is another such antibody, also in small-scale Phase II clinical trials, that is being used to reduce myocardial damage in patients undergoing percutaneous coronary intervention (PCI). There are currently no cancer clinical trials that include these P-selectin antibodies.

## 5.4 Conclusions

While great strides forward have been made in the detection and treatment of various cancer types, cancer metastasis remains a difficult puzzle to investigate. Research on resected tumors must be focused in more closely on portions of the leading edge which likely have genetic and proteomic profiles much different from that of cells within other parts of the tumor. Epigenetic changes are likely as important as genetic changes and must be considered in concert. As global gene and protein expression microarray technology and live *in vivo* imaging become more widely available for basic research purposes, our understanding of metastasis will hopefully advance more rapidly.

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# Chapter 6

## Anti-cancer Drugs – Discovery, Development and Therapy



Wolfgang Link

**Abstract** The most widely used treatments for cancer are surgery, radiotherapy and chemotherapy. Chemotherapy is the only option for metastatic cancers, where the treatment has to be systemic. The most frequently used chemotherapy drugs have been identified empirically without any pre-existing knowledge regarding the molecular mechanism of action of the drugs. Despite the remarkable progress achieved in cancer care and research over the past several decades, the treatment options for the majority of epithelial cancers have not changed much. However, a critical mass of knowledge has been accumulated that may transform cancer treatments from cytotoxic regimens towards the rapidly dividing cells into personalized targeted therapies. This chapter will provide an overview of currently used chemotherapeutics and will explore the impact of the molecular understanding of cancer on modern drug discovery, drug development and cancer therapy.

**Keywords** Cancer · Chemotherapy · Targeted therapy · Drug discovery and development · Preclinical development · Clinical trials

The most widely used treatments for cancer are surgery, radiotherapy and chemotherapy. Chemotherapy is the only option for metastatic cancers, where the treatment has to be systemic. The most frequently used chemotherapy drugs have been identified empirically without any pre-existing knowledge regarding the molecular mechanism of action of the drugs. Despite the remarkable progress achieved in

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cancer care and research over the past several decades, the treatment options for the majority of epithelial cancers have not changed much. However, a critical mass of knowledge has been accumulated that may transform cancer treatments from cytotoxic regimens towards the rapidly dividing cells into personalized targeted therapies. This chapter will provide an overview of currently used chemotherapeutics and will explore the impact of the molecular understanding of cancer on modern drug discovery, drug development and cancer therapy.

## 6.1 Introduction

Despite significant progress in the understanding of cancer biology there is a persistent lack of progress in curing most metastatic forms of cancer. Among the standard treatment options for human cancers which include surgery, radiation therapy, immunotherapy and chemotherapy, the latter one is often the only option for treatment of metastatic disease where treatment has to be systemic throughout the entire body. Chemotherapy is the use of chemical agents for the treatment of cancer. Most chemotherapeutic agents exert their cytotoxic effect by modifying DNA, by acting as fraudulent mimics of DNA components, by inhibiting enzymes involved in DNA synthesis or by blocking cell division. Traditional chemotherapy kills cells that are rapidly dividing, regardless if they are cancer cells or not. Therefore standard chemotherapy damages healthy tissues, especially those that display a high replacement rate. Over the past few decades efforts in cancer research has paved the way for better therapies that interfere with specific targeted molecules. These treatments are called targeted therapies and hold promise to improve clinical outcomes without the toxicity associated with traditional chemotherapy. The transformation of the accumulated knowledge in cancer biology into clinical practice represents a major challenge for the scientific community and pharmaceutical industry.

## 6.2 Conventional Chemotherapy

### 6.2.1 *The Origin of Chemotherapy*

The origin of chemotherapy dates back to the early 1940s when the toxic action of nitrogen mustard-based war gas on cells of the haematopoietic system was discovered. Researchers at Yale University demonstrated the anticancer activity of mustard agents in a murine lymphoma model and then in a patient who had non-Hodgkin's lymphoma. The results of these studies conducted in 1943 were published in 1946. Nitrogen mustards are DNA alkylating agents that attach an alkyl group (R-CH<sub>2</sub>) to the guanine base of DNA and interfere with DNA replication.

## 6.2.2 The Classification of Traditional Chemotherapy

Nowadays, many different alkylating agents are given as part of anticancer therapy regimes. In addition a broad range of non-alkylating drugs have been developed to treat cancer. All current chemotherapeutic drugs can be classified into several categories according to their mechanism of action: (1) DNA-modifying agents (alkylating agents and alkylating-like agents), (2) anti-metabolites (that imitate the role of purines or pyrimidines as building blocks of DNA), (3), spindle poisons (typically plant alkaloids and terpenoids that block cell division by inhibiting microtubule function), (4) topoisomerase inhibitors (preventing transcription and replication of DNA) and (5) cytotoxic antibiotics (for example anthracycline, that inhibit DNA and RNA synthesis thus block topoisomerase. Table 6.1 shows examples of each category. Chemotherapy agents can also be classified into cell cycle specific and cell cycle non-specific drugs. Most chemotherapeutic drugs are cell cycle-specific and act on cells undergoing division. Cell cycle-specific drugs can be subdivided into S-phase- G1-phase-, G2 phase- and M-phase-specific agents according to the phase of the cell cycle in which they are active. Antimetabolites are most active during the S phase of cell cycle because they exert their cytotoxic activity by inhibiting DNA synthesis. Conversely, vinca alkaloids which inhibit spindle formation and alignment of chromosomes are M-phase specific. Cell cycle-specific drugs are most effective for high growth fraction malignancies (e.g.: hematologic cancers). Their capability to kill cells displays a dose-related plateau and does not increase with further increased dosage, because at a certain time point only a subset of cells is fully drug sensitive. In contrast, cell cycle non-specific drugs such as alkylating

**Table 6.1** Conventional chemotherapeutic agents classified according to their mode of action

Type of agent	Examples	Mode of action	Affected cell cycle phase
<b>DNA-modifying agents</b>			
Alkylating agents	Chlorambucil	Alkylation of DNA	Phase nonspecific
	Cyclophosphamide	Alkylation of DNA	Phase nonspecific
	Carmustine	Alkylation of DNA	Phase nonspecific
	Lomustine	Alkylation of DNA	Phase nonspecific
	Dacarbazine	Alkylation of DNA	Phase nonspecific
	Temozolomide	Alkylation of DNA	Phase nonspecific
Platinum complexes	Cisplatin	DNA adduct formation	Phase nonspecific
	Oxaliplatin	DNA adduct formation	Phase nonspecific
	Carboplatin	DNA adduct formation	Phase nonspecific
<b>Anti-metabolites</b>			
	Methotrexate	Folic acid antagonist	S-Phase
	6-Mercaptopurine	Inhibits nucleotide synthesis	S-Phase
	Fluorouracil	Inhibits synthesis of nucleic acids	S-Phase
	Gemcitabine	Incorporated into DNA/Interfere with DNA synthesis	S-Phase
<b>Spindle poisons</b>			
Vinca alkaloids	Vinblastine	Prevent microtubule assembly	M-Phase
	Vincristine	Prevent microtubule assembly	M-Phase
Taxanes	Paclitaxel	Prevent microtubule disassembly	M-Phase
	Docetaxel	Prevent microtubule disassembly	M-Phase
<b>Topoisomerase inhibitors</b>			
Topoisomerase I inhibitors	Camptothecin	Causes strand breaks/Inhibits DNA replication	G2 phase
Topoisomerase II inhibitors	Etoposide	Inhibits DNA replication	M-Phase
	Topotecan	Inhibits DNA replication	M-Phase
<b>Antitumor antibiotics</b>			
	Bleomycin	Causes DNA fragmentation	G2 phase
	Daunorubicin	intercalate with DNA/inhibit topoisomerase II	S-Phase
	Doxorubicin	intercalate with DNA/inhibit topoisomerase II	S-Phase

agents have a linear dose-response curve and affect cells regardless whether they are proliferating or resting. They are effective for both low and high growth fraction tumors.

### ***6.2.3 The Limitations of Traditional Chemotherapy***

The success of cancer chemotherapy is limited by problems with toxicity, efficacy and drug resistance. As most conventional chemotherapeutic agents also affect rapidly dividing cells in healthy tissues they can cause severe side effects, in particular myelosuppression, immunosuppression, alopecia, mucositis, nausea and vomiting, diarrhea and flu-like symptoms. The cytotoxic effect of conventional chemotherapy affects resting cells, e.g., cancer stem cells less effectively. Therefore, the drug might be very efficient against cells that form the bulk of the tumor, that are not able to form new cells but does not affect the rare subpopulation of cancer cells which can repopulate the tumor and cause relapse. In addition, traditional chemotherapeutic agents target cell proliferation with little effect on other important hallmarks of cancers such as angiogenesis, invasion and metastases. A major problem associated with anticancer drugs (traditional and targeted therapies) is drug resistance. Some tumors, in particular pancreatic cancer, renal cell cancer, brain cancer and melanoma exhibit absence of response on the first exposure to standard agents (primary resistance). Conversely, some drug-sensitive tumors acquire resistance during the course of the treatment (acquired resistance). Drug resistance can be classified into drug-specific resistance and multi-drug resistance. Whereas drug-specific resistance is usually mediated by specific genetic alterations, the multi-drug resistant phenotype is often associated with increased expression of P-glycoprotein which expels drugs from the cell.

### ***6.2.4 Targeted Therapies***

Targeted therapeutic agents interact with a specific molecular target to mediate their therapeutic effects. These molecular targets have been identified and validated through careful research as part of pathways and processes that drive tumor formation and progression. A therapeutic target is a cellular macromolecule that is involved in the pathogenesis of the disease, druggable (undergoes a specific interaction with a drug) and its pharmacological modulation has an effect on the course of the disease. There are four main types of drug targets: proteins, polysaccharides, lipids, and nucleic acids. Proteins are considered the best source of drug targets as most known drugs have been shown to interact with them.

Targeted therapeutic drugs can be classified into small molecules, [antibodies](#), and [vaccines](#). Small molecules are defined as molecules below a molecular weight of 900 Daltons. They rapidly diffuse across cell membranes and can reach intracel-

lular targets as well as targets located outside the cell. Several small-molecule kinase inhibitors have been approved for clinical use. Conversely, monoclonal antibodies cannot cross cell membranes and act on the outside of a cell. They can inhibit the interaction of signaling molecules and receptors or trigger an immune response to kill cancer cells. Alternatively, monoclonal antibodies coupled to toxic agents or radioactive molecules can be used to guide cytotoxicity specifically to cancer cells. Therapeutic cancer vaccines activate the body's immune system to attack cancer cells. These cancer vaccines usually contain antigens that are specific or overexpressed in cancer cells. As many of these antigens are also present on normal cells, self tolerance has to be suppressed to obtain an effective antitumor immune response. This strategy is viable as long as the normal tissue is nonessential. Examples include antigens such as tyrosinase, MART-1, gp100, and TRP-1, which are expressed on melanoma cells as well as normal melanocytes.

### **6.2.5 *Imatinib (Gleevec)***

The small molecule kinase inhibitor Imatinib emerged as a paradigm for molecularly targeted therapies. Gleevec was introduced in 2001 for the treatment of Chronic Myelogenous Leukaemia (CML). CML is a cancer of the white blood cells caused by the reciprocal translocation between chromosome 9 and chromosome 22. The resulting Philadelphia chromosome contains the fusion of the Bcr and Abl genes that gives rise to a constitutively active tyrosine kinase enzyme. Imatinib prevents signal transduction of BCR-ABL by binding to its ATP binding site. This prevents the transfer of phosphate groups from ATP to a protein substrate and suppresses cell growth and division. The success of Imatinib has proven that the concept of targeting specific molecular events in cancer can result in highly efficient anticancer therapies. Nevertheless, as CML is a genetically simple neoplasm caused by a single aberrant protein there is still substantial debate about whether the Imatinib-paradigm can be translated to other cancers which are caused by a multitude of complex interacting genetic and environmental factors.

### **6.2.6 *Trastuzumab (Herceptin)***

The monoclonal antibody Trastuzumab (Herceptin) inhibits the activity of the growth factor receptor HER-2 which is required for cell growth in normal breast tissue. HER-2 is overexpressed in 30% of breast cancer patients either by transcriptional activation or gene amplification contributing to cancerous cell growth. Trastuzumab binds to HER-2 at the cell surface and prevents HER-2 mediated growth stimulatory downstream signaling. As a result disease progression is slowed down. However, 70% of breast cancer patients (with HER-2 negative tumors) would not benefit from the treatment with Trastuzumab which is expensive and associated

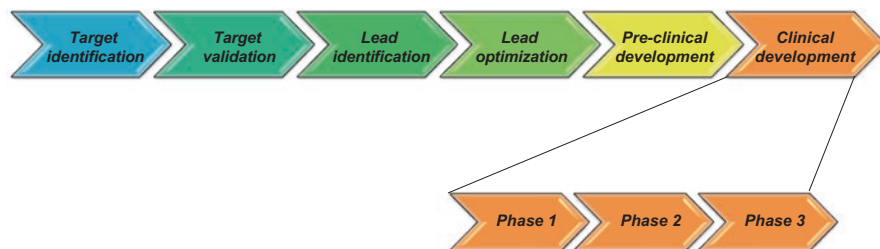
with adverse effects. This is a good example for the fact that many targeted therapies require companion diagnostic biomarkers to identify the subset of patients that would benefit from the corresponding targeted drug. In the case of Trastuzumab, several companion diagnostic test that detect the overexpression of HER-2 by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) have been approved by the US Food and Drug Administration (FDA).

### ***6.2.7 The Limitations of Targeted Therapies***

Targeted therapies have been introduced in recent years and at present the impact is limited to some specific types of cancer. These are still early days to judge whether targeted therapies will mark a true breakthrough in cancer treatment. The widespread optimism is not shared by everyone, however. It has been argued that most targeted therapies offer only marginal extensions of life and few cures. Considering the enormous costs of these treatments, gains are rather modest. Some researchers suggest that we should focus more on metabolic and oxidative vulnerabilities that arise as a consequence of the uncontrolled growth and proliferation capacities of all cancer cells, rather than on targeting molecular events specific only for a small subset of a given cancer type. It is important to note that intrinsic or acquired resistance still limits the efficacy of targeted therapies in cancer treatment. Selective pressure in combination with mutations, epigenetic alterations or changes in microenvironment lead to resistant cancer cells and in turn to tumor regrowth and clinical relapse. As the malignant phenotype is often regulated by multiple parallel pathways the cancer cell may start to use alternative rescue signaling, if the main route has been targeted by an inhibitor. Therefore it might be useful to block several supporting pathways using combination therapies with other anticancer agents to prevent resistance development. Importantly, the determination of resistance mechanisms can provide the basis for the design of second-generation therapies. This strategy has been successfully employed to inhibit BCR-ABL with imatinib resistant point mutations using the second-generation kinase inhibitor dasatinib (SPRYCEL).

### ***6.2.8 Discovery and Development of Targeted Therapies***

The important progress in the molecular understanding of cancer which has been made during the last three decades has profoundly transformed the way we identify and develop anticancer drugs. Nowadays, drug discovery and drug development is a long and expensive process. It takes an average of 12 years and costs about 800 million US dollars to get a new drug from the laboratory to the pharmacy shelf. The process consists of several sequential steps: (1) Target identification, (2) Target validation, (3) Lead identification, (4) Lead optimization, (5) Pre-clinical development and (6) Clinical development (Fig. 6.1).



**Fig. 6.1** Flow chart of the drug discovery and development process. The process consists of several sequential steps including target identification, target validation, lead identification, lead optimization, pre-clinical development and clinical development. Clinical development is carried out in three phases before a new drug can be approved for commercialization

### 6.2.9 Target Identification

The identification and validation of disease relevant targets are crucial for the development of molecularly targeted anticancer therapies. However, without a thorough understanding of the molecular events driving tumor formation and progression it is difficult to identify therapeutically useful targets. Therefore, these targets often emerge from research laboratories of the nonprofit and public sectors such as university and government laboratories. An ideal molecular target for an anticancer drug is specific and essential for the cancer cell. That means that it is absent in normal cells and necessary for tumor formation and progression just as the bacterial cell wall, as the target of penicillin is specific for the bacterium (not present in humans) and essential for its viability. As cancer cells evolve from normal cells most cancers do not possess molecular targets comparable to the bacterial cell wall. Therefore cancer research aims to identify targets that are to some degree essential and specific to cancer cells versus normal cells for example a protein that present an increased expression in cancer cells compared to normal cells (Table 6.2).

### 6.2.10 Target Validation

Protein overexpression in cancer cells might represent a defensive mechanism against tumorigenesis or occur completely unrelated. The fact that a correlation does not establish causation is illustrated by the following example: firemen are found at burning houses, but firemen are not found at normal houses. Therefore, firemen cause house fire and therefore, we should eliminate firemen to prevent fires. In order to confirm molecules as useful therapeutic targets the disease relevance has to be established. Target validation is the process of establishing a disease-causative effect and the therapeutic potential of a potential target. Target validation involves a variety of methods including genetic, cell-based, and animal models. TaqMan, in situ hybridization, western blotting and immunohistochemistry can be used to

**Table 6.2** Targeted anticancer agents

Drug (Trade name)	Drug type	Target(s)	Disease indication
Alemtuzumab (Campath-1H®)	Antibody	CD52,	CLL, CTCL, T-cell lymphoma
Bevacizumab (Avastin®)	Antibody	VEGF	Glioblastoma and colorectal cancer
Bortezomib (Velcade®)	Small molecule	Proteasome	Multiple myeloma/MCL
Cetuximab (Erbix®)	Antibody	EGFR	SCC and colorectal cancer
Dasatinib (Sprycel®)	Small molecule	BCR/ABL, Src family	CML and ALL
Erlotinib (Tarceva®)	Small molecule	EGFR	NSCLC and pancreatic cancer
Gefitinib (Iressa®)	Small molecule	EGFR	NSCLC
Gemtuzumab (Mylotarg®)	Antibody/immunotoxin	CD33	AML
Ibrutinib (Imbruvica®)	Small molecule	BTk	MCL, CLL
Imatinib (Gleevec®)	Small molecule	ABL and c-KIT	CML
Ipilimumab (YERVOY®)	Antibody	CTLA-4	Melanoma
Rituximab (Rituxan®)	Antibody	CD20	Non-Hodgkin lymphoma and CLL
Sorafenib (Nexavar®)	Small molecule	VEGFR, PDGFR and C-Raf	RCC
Temsirolimus (Torisel®)	Small molecule	mTOR	RCC
Tositumomab (Bexxar®)	Antibody/immunotoxin	CD20	Non-Hodgkin lymphoma
Trastuzumab (Herceptin®)	Antibody	HER2	Breast cancer
Vemurafenib (Zelboraf®)	Small molecule	BRAF V600E	Melanoma
Vismodegib (Erivedge®)	Small molecule	Smoothed (SMO)	BCC
Vorinostat (Zolinza®)	Small molecule	HDAC	CTCL

Abbreviations: *AML* acute myeloid leukemia, *ALL* acute lymphocytic leukaemia, *BCC* basal-cell carcinoma, *BTk* Bruton's tyrosine kinase, *CLL* chronic lymphocytic leukemia, *CTCL* cutaneous T-cell lymphoma, *CTLA-4* cytotoxic T-lymphocyte-associated antigen-4, *GIST* gastrointestinal stromal tumor, *HDACs* histone deacetylases, *NSCLC* non-small cell lung cancer, *MCL* mantle cell lymphoma, *RCC* renal cell carcinoma, *SCC* squamous cell carcinoma, *VEGF* vascular endothelial growth factor

determine mRNA or protein expression of the target in normal vs. disease tissues. Direct modulation of target activity can be achieved by RNA interference, antibodies, peptides, and tool compounds and provides functional insights. In vivo target manipulation using transgenic and knock-out/knock-in mouse models is an essential approach for functional validation and to prove disease relevance. An important aspect of these experiments is to explore the potential adverse consequences of modulating the target. In addition, population-based genetic studies can provide evidence for the significance of the target in the population where the disease occurs. Careful validation of the potential drug target is extremely important as any efforts expended on developing a drug on a poorly validated target will probably lead to its failure in clinical trials due to a lack of efficacy. A cancer drug target is only truly validated by demonstrating that a given therapeutic agent is clinically effective and acts through the target against which it was designed.

### 6.2.11 Lead Identification

Once the potential drug target has been validated, a biochemical or cell-based assay to monitor target activity is developed. Assay developers adapt the assay to a multi-well format to test many different treatments in parallel. The quality and consistency of the assay is determined by calculation the *Z'* factor. This metric describes the available signal window for an assay in terms of the total separation between negative and positive controls minus the error associated with each type of control.

A  $Z'$  value greater than 0.5 is considered as acceptable for high-throughput screening (HTS). Screening is the testing a random and large number of different molecules for biological activity. Many different collections of chemical compounds, called compound libraries for HTS are commercially available or owned by pharmaceutical companies. If the protein to be targeted is for example a kinase involved in a cancer signaling pathway, then rather than screening a complex library of diverse compounds, a focused chemical library would be constructed to target the ATP binding sites on the kinase enzyme. The active compounds from the primary screening known as hits are then analyzed in subsequent confirmation screens and counter screens to identify leads. This step in early drug discovery is referred to as the “hit-to-lead” process. A lead compound is a chemical molecule that demonstrates desired biological activity on a validated molecular target. Its chemical structure is used as a starting point for chemical modifications. In addition to the screening approach, there are several alternative strategies that can be used to identify lead compounds. A starting point is often an interesting bioactive compound which is chemically modified to improve its biological activity or pharmacokinetic properties or to strengthen intellectual property position. An increasingly important strategy in modern drug discovery is rational drug design. Rational drug design begins with the design of compounds that conform to specific requirements coming either from the 3D structure of biological target (structure -based drug design) or from structures of known active small molecules (ligand-based drug design). Lastly, even in modern drug discovery serendipity (luck) is still an important factor as the development of Viagra to treat erectile dysfunction illustrates.

### **6.2.12 Lead Optimization**

The difference between a good ligand and a successful drug is that the latter is not only potent against the intended target (as a good ligand), but also exhibits good physical and chemical properties. The concept of druglikeness defines several structural features which determine whether a molecule is similar to known drugs. Assessment of druglikeness usually follows the Lipinski's rule of five (see Box 6.1). Newly identified compounds may have poor druglikeness and may require chemical modification to become drug-like enough to be tested biologically or clinically. During the lead optimization process medicinal chemists attempt to improve the physical and chemical properties of a lead compound introducing small structural modifications. Importantly, a successful drug must be absorbed into the bloodstream, distributed to the proper site of action in the body, metabolized efficiently and effectively and successfully excreted from the body. These pharmacokinetic or ADME (Absorption, Distribution, Metabolism and Excretion) properties describe the disposition of a compound within an organism and influence the activity of the compound as a drug. In modern drug discovery ADME properties of lead compounds are determined in early phases using relatively simple in vitro assays to



**Box 6.1: Lipinski's Rule of Five**

Lipinski's rule of five (there are only 4 rules) is a guideline to determine if a chemical compound has properties that would make it a likely orally active drug in humans. Christopher Lipinski, a medicinal chemist at Pfizer analyzed the physical and chemical properties of marketed drugs. He formulated the rule in 1997 based on the observation that most medication drugs are relatively small and lipophilic molecules. In fact most of them (87%) satisfy all Lipinski's rules:

1. <5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
2. <10 hydrogen bond acceptors (all nitrogen or oxygen atoms).
3. A molecular mass < 500 daltons.
4. log P (octanol-water partition coefficient) < 5

All values are multiples of five (origin of the rule's name)

guide medicinal chemistry during lead optimization. Early ADME assays assess the solubility, lipophilicity, membrane permeability and metabolic stability of the lead compound as well as its capacity to bind plasma proteins and inhibit or induce enzymes that are essential for the metabolism of many drugs (indicative of possible drug-drug interactions). The lead optimization process consists of iterative cycles of chemical design and biological assessment aimed at the selection of a drug candidate for preclinical development.

### 6.2.13 *Pre-clinical Development*

Preclinical development is the process of taking an optimized lead through the stages necessary to allow human testing. Preclinical development includes in vitro and in vivo experiments to determine safety and efficacy of the drug candidate. During preclinical development, researchers must work out how to make large enough quantities of the drug for clinical trials. Efficacy evaluation of an anticancer drug candidate involves testing the impact on the viability of a broad variety of cancer cell lines, xenograft experiments in nude mice and experiments in more sophisticated genetically engineered mouse models. One of the major challenges in drug development is the accurate prediction of drug toxicity in humans. The standard approach to toxicity testing includes acute, subchronic, chronic exposure in three animal species. Regulatory authorities usually require that drugs are tested in both a rodent and a non-rodent mammalian species. Usually, these tests are carried out in mice, rats and dogs. Drugs with toxicity only in humans and not in non-human animals should be detected in the clinical trials. Unfortunately, due to

several limitations in the design of clinical trials this is not always the case. That is one of the reasons why 2.9% of the marketed drugs were withdrawn from the market during the last four decades. Pre-clinical studies must be conducted according to stringent good laboratory practices (GLPs), which require meticulous control and recording of processes. Before any clinical trial can begin, the sponsor, usually a pharmaceutical company must obtain permission to test the candidate drug in humans filing an Investigational New Drug (IND) application. The application is reviewed by regulatory authorities to make sure people participating in the clinical trials will not be exposed to unreasonable risks. Studies in humans can only begin after IND is approved.

## **6.3 Clinical Development**

Clinical trials serve as the basis for evidence-based medicine and are conducted in three phases of development before a new drug can be approved for commercialization.

### ***6.3.1 Phase 1 Clinical Trials***

A phase 1 clinical trial (also called first in humans, FIH) is the first step in testing a new investigational drug or new use of a marketed drug in humans. Oncology phase 1 trials typically involve 20–80 patients with advanced cancer that has not responded to standard cancer treatments. In phase 1 clinical studies emphasis is put on drug safety. A principal goal of this phase is to establish a dose and/or schedule of a candidate drug for testing its efficacy in phase 2 trials. Trial participants are divided into small groups, known as cohorts. The first cohort receives a low dose of the new drug. In the absence of any major adverse side effects, the dose is escalated until pre-determined safety levels are reached, or intolerable side effects start showing up. Drug induced toxicity is analyzed relative to the dose and unexpected side effects are explored. Furthermore, researchers characterize the metabolism and routes of excretion of the candidate drug. Phase 1 clinical trials last about 1 year. About 70% of drugs pass this phase.

### ***6.3.2 Phase 2 Clinical Trials***

In Phase 2, the candidate drug is tested to see if it has any beneficial effect and to determine the dose level needed for this effect. Phase 2 clinical trials are clinical studies on a limited scale focused on efficacy. They typically involve 100–300 individuals who have the target disease and may be done at multiple sites to enhance

recruiting. As the success of targeted anticancer treatments depends on the presence of a specific molecular target, the selection of suitable patients is key for testing these agents in phase 2 clinical trials. Patients receiving the drug are compared to similar patients receiving a placebo or another drug. The efficacy of a candidate drug in clinical trials is measured by means of certain predetermined endpoints such as overall survival or progression free survival. An increasingly important aspect in phase 2 trials for targeted agents is the development of mechanism-based biomarker to determine if the candidate drug affects the intended target. Phase 2 clinical trials last about 2 years. About 33% of drugs pass this phase.

### **6.3.3 Phase 3 Clinical Trials**

Phase 3 clinical trials are comparative studies on large number of patients to demonstrate that the candidate drug works. In order to generate statistically significant data about safety and efficacy phase 3 clinical trials are conducted as multi-center (conducted at more than one medical center), randomized (patients are randomly allocated to receive one or other of the alternative treatments) and double-blind (neither the participants nor the researchers know who is receiving a particular treatment) controlled studies. Phase 3 clinical trials typically involve 1000–3000 patients. The drug candidate is compared with existing treatments focused on safety and efficacy. Phase 3 clinical trials should characterize the effect of the candidate drug in different populations considering patient variations in genetics, life style and concomitant conditions such as liver impairment or pregnancy using different dosages as well as combined treatment with other drugs. Phase 3 clinical trials should confirm therapeutic efficacy in the target population and determine the safety profile. It also provides the basis for labeling instructions to ensure proper use of the drug. Phase 3 clinical trials last about 3 years. About 25–30% of drugs pass this phase.

### **6.3.4 Drug Approval**

All new drugs have to be approved by regulatory authorities such as the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in the European Union. These agencies evaluate new drugs based on the evidence presented from the clinical studies. These data is provided by the sponsor in the so called “New Drug Application” (NDA). After NDA approval is obtained, the pharmaceutical company will market the drug. To be approved, a new drug has to be non-inferior or better than an approved drug. Non-inferior outcome ensures that a survival advantage associated with an approved drug will not be lost with a new agent.

## 6.4 Conclusions

A better molecular understanding of cancer has enabled the development of targeted therapies. Unlike conventional chemotherapeutic drugs that kill rapidly dividing cells by affecting DNA replication and cell division, targeted agents interfere with specific molecular targets that are critical for tumor formation and progression. The advent of targeted therapies has profoundly transformed the drug discovery and development process. The identification and rigorous validation of disease relevant molecular targets are among the most critical activities for successful development of targeted anti-cancer agents. The challenges associated with targeted therapies also apply to the subsequent phases of the drug development process. In particular, the development of companion diagnostic tests to identify patient populations that are most likely to benefit from the treatment are essential for the success in clinical efficacy studies. Emerging resistance to targeted therapies can be addressed by second-generation agents or combination therapies to prevent resistance or restore response.

- 1. Which of the following drugs is an alkylating agent?**
  - A. Paclitaxel
  - B. 5-Fluorouracil
  - C. Dacarbazine
  - D. Doxorubicin
  - E. Topotecan
- 2. Chemotherapy agents can be classified into cell cycle specific and cell cycle non-specific drugs. Which of the following statements about vinca alkaloids is correct?**
  - A. Vinca alkaloids block cell division by inhibiting microtubule function and are G1-phase specific
  - B. Vinca alkaloids which inhibit spindle formation and alignment of chromosomes are M-phase specific
  - C. Vinca alkaloids are cell cycle non-specific drugs as they inhibit spindle formation and alignment of chromosomes
  - D. Vinca alkaloids are most active during the S phase of cell cycle because they exert their cytotoxic activity by inhibiting DNA synthesis
  - E. Vinca alkaloids prevent transcription and replication of DNA and are most active during G1-phase and G2 phase
- 3. A signaling protein inside the cell is mutated and hence constitutively active driving cell proliferation, and resulting in the formation of a tumor. What type of targeted therapy might be effective?**
  - A. Monoclonal antibody that prevents growth factors from interacting with the receptor

- B. Monoclonal antibody that holds the growth factor receptor in the “OFF” position
  - C. Small molecule that selectively binds to the mutated protein
  - D. Monoclonal antibody that selectively binds to the mutated protein
4. **What is meant by a lead compound in medicinal chemistry?**
- A. A drug containing the element lead
  - B. A leading drug in a particular area of medicine
  - C. A compound that acts as a starting point for drug development
  - D. A drug which is normally the first to be described for a particular disease/aliment
5. **Which of the following statements is one of the Lipinski’s rules (Rule of Five)?**
- A. An orally active drug has a molecular weight equal to 500
  - B. An orally active drug has no more than five hydrogen bond acceptor groups
  - C. An orally active drug has no more than 10 hydrogen bond donor groups
  - D. An orally active drug has a calculated logP value less than +5
6. **Which of the following objectives in drug development is not related to pharmacodynamics?**
- A. The reduction of side effects
  - B. The optimization of activity
  - C. The reduction of toxicity
  - D. The maximization of oral bioavailability
7. **Pharmacokinetics is defined as**
- A. The study of biological and therapeutic effects of drugs
  - B. The study of absorption, distribution, metabolism and excretion of drugs
  - C. The study of mechanisms of drug action
  - D. The study of methods of new drug development
8. **Which of the following types of clinical trials determines whether a targeted therapy works against cancer?**
- A. Phase I
  - B. Phase II
  - C. Phase III
  - D. Phase II and Phase III
  - E. Phase I, Phase II, and Phase III

### Answers

1. **Which of the following drugs is an alkylating agent?**
- A. Paclitaxel
  - B. 5-Fluorouracil
  - C. **Dacarbazine**
  - D. Doxorubicin
  - E. Topotecan

Paclitaxel, 5-Fluorouracil, Doxorubicin, Topotecan are not alkylating agent, they act through different modes of action. Paclitaxel prevent microtubule disassembly, 5-Fluorouracil is an anti-metabolite, Topotecan and Doxorubicin are topoisomerase II inhibitors

2. **Chemotherapy agents can be classified into cell cycle specific and cell cycle non-specific drugs. Which of the following statements about vinca alkaloids is correct?**

- A. Vinca alkaloids block cell division by inhibiting microtubule function and are G1-phase specific
- B. **Vinca alkaloids which inhibit spindle formation and alignment of chromosomes are M-phase specific**
- C. Vinca alkaloids are cell cycle non-specific drugs as they inhibit spindle formation and alignment of chromosomes
- D. Vinca alkaloids are most active during the S phase of cell cycle because they exert their cytotoxic activity by inhibiting DNA synthesis
- E. Vinca alkaloids prevent transcription and replication of DNA and are most active during G1-phase and G2 phase

Vinca alkaloids are cell cycle specific. They inhibit spindle formation and alignment of chromosomes most important during M-phase of the cell cycle.

3. **A signaling protein inside the cell is mutated and hence constitutively active driving cell proliferation, and resulting in the formation of a tumor. What type of targeted therapy might be effective?**

- A. Monoclonal antibody that prevents growth factors from interacting with the receptor
- B. Monoclonal antibody that holds the growth factor receptor in the “OFF” position
- C. **Small molecule that selectively binds to the mutated protein**
- D. Monoclonal antibody that selectively binds to the mutated protein

Most small molecule can pass the plasma membrane and act inside the cell

4. **What is meant by a lead compound in medicinal chemistry?**

- A. A drug containing the element lead
- B. A leading drug in a particular area of medicine
- C. **A compound that acts as a starting point for drug development**
- D. A drug which is normally the first to be described for a particular disease/aliment

Lead compound is a biologically active, drug like molecule which suitable for the lead optimization process in drug development

5. **Which of the following statements is one of the Lipinski's rules (Rule of Five)?**
- A. An orally active drug has a molecular weight equal to 500
  - B. An orally active drug has no more than five hydrogen bond acceptor groups
  - C. An orally active drug has no more than 10 hydrogen bond donor groups
  - D. **An orally active drug has a calculated logP value less than +5**

Lipinski's rules are:

1. <5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
  2. <10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
  3. A molecular mass < 500 daltons
  4. log P (octanol-water partition coefficient) < 5
6. **Which of the following objectives in drug development is not related to pharmacodynamics?**
- A. The reduction of side effects
  - B. The optimization of activity
  - C. The reduction of toxicity
  - D. **The maximization of oral bioavailability**

Oral bioavailability is part of Pharmacokinetics

7. **Pharmacokinetics is defined as**
- A. The study of biological and therapeutic effects of drugs
  - B. **The study of absorption, distribution, metabolism and excretion of drugs**
  - C. The study of mechanisms of drug action
  - D. The study of methods of new drug development

Pharmacokinetics is related to the impact of the body on the drug, in other words how the drug is absorbed, distributed, metabolized and excreted

8. **Which of the following types of clinical trials determines whether a targeted therapy works against cancer?**
- A. Phase I
  - B. Phase II
  - C. Phase III
  - D. **Phase II and Phase III**
  - E. Phase I, Phase II, and Phase III

Clinical phase I trials focus on drug safety, Phase II on efficacy and Phase III on efficacy and safety

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# Chapter 7

## Principles of Immuno-Oncology



Ana Mafalda Saraiva, Ramon Andrade De Mello, and Pedro Madureira

**Abstract** The major function of the immune system is to initiate immunologic responses to protect the host against invading or infectious pathogens and to maintain homeostatic balance. The immune system also has an important role in anticancer response. There are numerous checkpoints that moderate immune responses, to repress autoimmunity and regulate the amplitude and duration of T cell responses. Since some tumours benefit from these checkpoint pathways to escape antitumour immune responses, the blockade of checkpoint molecules is being studied as a therapeutic anticancer strategy. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) are immune checkpoint pathways with the potential for therapeutic anticancer targeting.

**Keywords** Immunotherapy · PDL1 · MSI

### 7.1 Immune System and Cancer

The major function of the immune system is to initiate immunologic responses to protect the host against invading or infectious pathogens and to maintain homeostatic balance. The immune system also has an important role in anticancer response. There are numerous checkpoints that moderate immune responses, to repress autoimmunity and regulate the amplitude and duration of T cell responses. Since some tumours benefit from these checkpoint pathways to escape anti-tumour immune

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responses, the blockade of checkpoint molecules is being studied as a therapeutic anticancer strategy. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) are immune checkpoint pathways with the potential for therapeutic anticancer targeting [9, 37].

CTLA4 is an immune checkpoint molecule expressed on effector T cells and its function is to regulate, at an early stage, the amplitudes of T cell activation by binding to B7-1 (CD80) or B7-2 (CD86) with better affinity than CD28, and to stop potentially autoreactive T cells [4, 9].

The PD1 pathway limits the activity of T cells in peripheral tissues throughout an inflammatory response, limiting excessive immune responses, such as autoimmune reactions, through binding to its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) [4, 31].

## 7.2 Innate Mechanisms of Response to Threats

### 7.2.1 *Cancer Immunoediting from Immune Surveillance to Immune Escape*

Given that cancer results from normal host cells and it is not an exogenous pathogen, achieving immunity to cancer does not fit properly into the self/nonself paradigm. Cancer antigens that are recognized by the human immune system are self-mutated molecules and this is the main difficulty that the immune system has in recognizing cancer cells properly.

The concept that the immune system could protect the host by recognizing and eliminating neoplastic diseases was first proposed by Paul Ehrlich. As the field of immunology began to develop, it provided the starting point upon which Burnet and Thomas based their cancer immunosurveillance hypothesis. This hypothesis considered that adaptive immunity was responsible for preventing cancer development in immunocompetent hosts [12, 32]. Most recently, it was demonstrated that the immune system further than including the elimination of primary nonviral cancers, also includes the sculpting of the immunogenic phenotypes of tumours that form in immunocompetent host, promoting tumour growth. This process can be summed up in three phases: elimination, equilibrium and escape, designated the “Three E’s” of cancer immunoediting [11, 12].

The elimination phase is the hallmark of the original concept of cancer immunosurveillance. In this phase, tumours cells are successfully eliminated, and it is involved both innate and adaptive responses of the immune system. The next step is the equilibrium phase in which occurs the sculpting of the tumour cells. This process leads to the immune selection of many genetically unstable and mutating tumour cells with reduced immunogenicity, facilitating tumours cells to resist the host’s immunological blockade. The last phase is called escape, where tumour cell variants selected in the previous phase can grow in an immunologically intact environment, allowing the tumours to expand and become clinically detectable [12, 22].

## 7.2.2 *First Events of “Danger” Recognition: Controversy to Dunn’s Theory*

Different from the self–non-self theory, the danger theory suggests that self components can trigger an immune response, if they are dangerous (e.g., cellular stress) and also that non-self components can be tolerated, if they are not dangerous (e.g., the fetus) [27]. Generally, tumour cells express antigens which should allow the immune system to eliminate them. Unfortunately, this does not occur, since tumours do not provide a danger signal for dendritic cells which do not activate the immune system, allowing the tumour cells to escape from the immune surveillance [23, 34].

Given this, we believe that the elimination phase, proposed by Dunn, is not occurring. That is, right from the beginning of the tumour formation, the immune system is able to recognize the malignant cells, but it is not at all capable of eliminating them effectively.

## 7.2.3 *Tumour Microenvironment*

Tumour cells develop in complex tissue environments and have the capability to modulate inflammatory responses and to adapt to microenvironment in which cancer evolves, promoting its growth.

A diversity of tumour-derived soluble factors (TDSFs) contributes to the emergence of immunosuppressive structure, such as VEGF, IL-10, TGF- $\beta$ , IL-6, prostaglandin E2 (PGE2), soluble FasL and MICA [22]. Some of these TDSFs play an important role in the recruitment and differentiation of immunosuppressive immune cell populations (Treg, NKT, iDC, MSC, and TAM); and also promote immunosuppressive metabolites, such as nitric oxide (through iNOS), adenosine (through hypoxia), or depletion of tryptophan (through IDO) and arginine (through Arginase). Tumour cells promote their own growth and neovascularisation by producing angiogenic and growth factors and in remodeling the extracellular matrix necessary for invasive and metastatic potential [19].

### 7.2.3.1 *Myeloid-Derived Suppressor Cells (MDSCs)*

Tumour-associated macrophages (TAM) are macrophages recruited to the tumour site. These cells interact with tumour cells and appear at the tumour–host tissue interface, in regions often associated with low oxygen tensions [33]. TAM cells can be proinflammatory with M1-type cells (classic activation), inhibiting the proliferation of surrounding cells and damage adjacent tissue; and may also be M2-like TAMs. M2-type macrophages release cytokines, promoting the proliferation of adjacent cells and tissue repair. Transforming growth factor- $\beta$  (TGF- $\beta$ ) and IL-10 give rise to M2-like functional phenotypes that have properties of high expression of mannose receptor,

IL-10 and angiogenic factors [2]. M2 macrophages express anti-inflammatory chemokines (CCL17, CCL22 and CCL24) favouring regulatory T cells (Treg), TH2 recruitment, favoring tumour growth and metastasis through immunosuppression [6].

### 7.3 Tregs Infiltration in Tumours

It already has been demonstrated in several studies that in various types of cancer accumulation of regulatory T cells (Tregs) in the tumour site is associated bad prognosis and reduction of patient survival. These cells maintain immunological self-tolerance by actively suppressing self-reactive lymphocytes [28]. Accumulation of Tregs expressing CD4, CD25 and FoxP3 inhibits T-cell activation through the production of IL-10 and TGF- $\beta$ , the expression of CTLA-4 and PD-L1, and the consumption of IL-2 [15]. This leads to an immunosuppressive function, resulting in immunological tolerance.

Treg cells and CTLA-4 are the predominant inhibitory cells and molecules of the immune system and some investigators believe that immune inhibitory state in lung cancer patients may be in part due to over expression of CTLA-4 and/or increase of Treg cells. A study conducted by Erfani *et al* demonstrated that the prevalence of Treg cells was significantly higher in patients with NSCLC than healthy donors. They also showed that the percentage of Treg cells in patients augmented by the increase in the stage of the disease and was also significantly higher in metastatic stage (IV) than non-metastatic stages [13]. Another study demonstrated that NSCLC tumour cells influence function of CD4<sup>+</sup> T cells from healthy donors, and that Tregs play a critical role in establishing and maintaining the immunosuppressive microenvironment of NSCLC. They established that NSCLC tumour cells demethylated the Foxp3 gene promoter, causing an enhanced transcription and expression of Foxp3 gene. These Foxp3<sup>+</sup> T cells were possibly being the reason for the secretion of immunosuppressive cytokines, such as IL-10 and TGF- $\beta$ 1, increasing immunosuppression in tumour bearing patients [21].

### 7.4 Immunotherapies: Two Sides of the Same Coin

Cancer immunotherapy is a rapidly evolving anticancer strategy that is based upon the growing wealth of evidence that immune surveillance and immune tolerance are key players in development and progression of cancer [32].

### 7.4.1 TKI

Protein tyrosine kinases (TKs) regulate signaling pathways concerning cellular proliferation, apoptosis, differentiation, function, and motility. Small molecule tyrosine kinases inhibitors (TKIs) are compounds designed to affect TK-dependent oncogenic pathways and are promising treatments for the therapy of many types of cancer. These agents potentially have a lower toxicity than conventional cytotoxic chemotherapy. However, some kinase inhibitors are less selective than originally thought and sometimes have an effect on multiple signaling pathways. With the use of TKIs, the study of side effects, such as resistance to these targeted therapies, became important [24, 26]. Resistance to TK inhibitors was first identified in patients with advanced **Chronic Myeloid Leukemia** (CML). Patients given imatinib relapsed and this was associated with point mutations that provided the ABL kinase resistant to the drug or, less commonly, was associated with BCR-ABL gene amplification [16]. Several strategies may help to prevent or overcome resistance to TK-targeted therapies. Combining monoclonal antibodies, cytotoxic chemotherapy, adoptive immunotherapy or tumour-cell vaccines with a TKI improves the sensitivity of tumour cells to immune-mediated killing, with the possibility of increasing the therapeutic efficacy of both treatments [24, 25].

### 7.4.2 Dendritic Cells

Numerous diseases concerning the immune system often impede the normal function of dendritic cells (DCs), namely microbial pathogens and tumors [35]. DCs can be key targets for therapeutic interventions in cancer, since they can capture tumour antigens and cross-present them to T cells. DCs [30]. Immunotherapy based on DCs has been used to produce tumour-specific antigen-presenting cells and to generate cytotoxic T lymphocyte responses against cancer cells [7]. Recent clinical studies of “first-generation” DC-based vaccines demonstrated that, regardless of their restricted activity in inducing regression of established cancer, they may help in prolonging the overall survival of cancer patients [20]. However, it has become apparent that DC-based therapy faces some obstacles. There are numerous different subsets of DCs, which have different cytokine profiles and functional features depending on generation or origin. As a result, it is fairly challenging to select and generate effective DCs for an explicit goal [8]. The two biggest obstacles that DC-based therapy are: the generation of enough numbers of functionally active DC in tumours, a condition that is vital [1]; and effective DC pulsing with real time tumour antigens [5]. To overcome these barriers some investigators studied the benefits of DC vaccination in combination with cytokine-induced killer (CIK) cancer therapy. The results showed that this combination was able to stimulate the patient’s immune systems against the cancer, by influencing the immune status of the patient [7, 36].

## 7.5 Chimeric-Antigen Receptor (CAR) T Cells

In the late 1980's Eshhar and colleagues engineered cytotoxic T lymphocytes to express a surface receptor constituted of the constant portion of the T cell receptor (TCR) and the variable fragment of an immunoglobulin specific for the hapten 2,4,6-trinitrophenil (TNP). Those chimeric T cells were activated by conjugated-TNP in an MHC-independent manner. This work laid the foundations for the use of CAR T cells for cancer immunotherapy [17].

The clear advantage of these T cells that bear a chimeric antigen receptor is to bypass the need of antigen presentation by MHC molecules, which are known to be down-regulated in many tumors [14].

Nowadays, CARs are formed from a combination of antibody-derived or ligand-derived domains and TCR domains. A CAR is commonly composed of an extracellular antibody single-chain variable fragment (scFv), a TCR-derived CD3 $\zeta$  domain and one or more intracellular co-stimulatory domains. Adoptive transfer of T cells expressing chimeric antigen receptors has shown to induce promising results in cancer therapy in humans. Adoptive transfer of CD19-directed CAR T (CART19) cells has generated considerable remissions in patients with refractory and relapsed B cell malignancies [3, 10, 18].

Adoptive transfer of CAR T cells requires that autologous T cells should be collected from the patient in order to avoid rejection from the own immune system. Briefly, patient's leukocytes are collected by leukapheresis and enriched in the desired phenotype (usually CD3<sup>+</sup>CD8<sup>+</sup>). The enriched lymphocyte population is then stimulated *in vitro* with a specified antigen presented by artificial beads and are transfected with the viral vector containing the gene for the expression of the chimeric antigen receptor. Upon selection of the cells expressing functional CARs, these cells are expanded for several days in bioreactors. Usually, the entire process can take 8–10 days [14].

Currently, several clinical trials are being conducted to test the efficacy of CAR T cells against different tumors. Initially, the use of CAR T cell adoptive therapy was thought mainly for hematological malignances, however, more recently, clinical trials to test the efficacy and safety of these therapies against solid tumors are also in place [Reviewed in [14]].

Although the initial stunning data obtained with adoptive CAR T cell therapy, one of the major concern raised with these therapies is that they can induce a massive production of inflammatory cytokines, leading to dramatic outcomes. This condition is known as cytokine-release syndrome [29].

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# Chapter 8

## Health Economics



Nelson Teich and Vanessa Teich

**Abstract** Health Care Costs have been increasing above Economic Growth in most of the countries of the world in the last decade, creating a significant challenge for the financing and incorporation of new technologies. Governments and Private Health Insurance Companies face consumer's increasing dissatisfaction with the Health Care that is delivered. A clear understanding of the critical clinical outcomes and of the efficiency of the Health Care Systems does not exist. The evaluation of new technologies and the decisions about their incorporation are done without taking into consideration the available budget and the opportunity costs. It is not simple for Health Care Professionals and Managers to see and measure the opportunity costs involved in the decisions that are made by them.

Health Economics is a Social Science that has the objective of giving Health Care Professionals and Managers the ability to navigate in this complex Health Care world and help them make the best choices and decisions for patients and society.

**Keywords** Health Economics · Oncology · Cancer · Opportunity costs · Budget · Scarce resources · Value · ICER · Net benefit · Health Care System · Efficiency · Costs · Clinical outcomes · Incorporation of technologies · Economic evaluation · QALY

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## 8.1 Introduction

Economics is a Social Science that studies how to make decisions under conditions of scarcity and how to allocate these scarce resources in a way that efficiency is maximised [1]. In Economics there is the critical concept of Opportunity Cost that means what is given up when we make choices about where to allocate human and financial resources [2, 3]. Using an example in Health Care, whenever a manager designates funds to a specific product, project or area, he or she is always giving up investments and possible benefits in other programs and populations. Those who make decisions about which programs to prioritize have to be careful not to underestimate the harms and problems that will occur with the choices that are made. An example in oncology is the incorporation of expensive drugs that result in small marginal improvements on survival and quality of life. What would be the benefit if this same amount of money were used in the prevention and early diagnosis? or to improve access to surgical curative procedures? or to improve the training and performance of Health Care Professionals?

Health Economics is the field of economics that has the objective of analysing and improving the efficiency of the Health Care System [4]. The less the financial resources societies and systems have, the most it is necessary to choose wisely to maximise Clinical Benefits and as a consequence improve the level of health and wellbeing. We can define Clinical benefit as a combination of increasing lifespan, improving quality of life, reducing years of life lived with disabilities and even giving patients access to diagnostic and therapeutic procedures in a more simple and comfortable way.

It is not uncommon for those who talk about Health Economics to associate and limit this science to Cost-effectiveness studies, but Health Economics goes beyond this and involves more than Cost-Effectiveness studies [5]. It is also common for people to refer to Health Economics as Pharmacoeconomics. This is also a very limited perception of Health Economics as an area of study and research.

## 8.2 Objectives of the Health Care System

Health Care Systems have the objective of maximising Life Expectancy, individual level of health, quality of life and wellbeing of citizens in a society. To achieve these objectives, it is critical to continuously measure and know with precision the clinical benefits and harms of preventive, diagnostic and therapeutic procedures to understand current efficiency and to define what should be discontinued, changed or incorporated and how; in order to permanently improve the System. The discussions and studies about what to incorporate have to be made anchored on the available financial resources [6]. One of the main problems that exist with Health Care Systems is when discussions, policies and choices are made as if the financial resources were unlimited. This type of behaviour creates unrealistic expectations

from patients, providers, managers and industries, ending up with not fulfilled promises and leading to disappointment with Health Care leaders, managers and Systems.

What is the essence and what are the objectives of the Health Care System?

It is necessary to understand what are the motivations and main objectives of the Health Care System and of their different players. The Health Care Systems can be patient-oriented or business oriented. This separation will help understand the strategies, choices, behaviour and actions of payers, providers and pharmaceutical, device and equipment industries. Ideally, this analysis should be done without bias or value judgment.

In a business-oriented system, the primary objective is to increase as much as possible the revenue and profitability of individuals, companies and institutions, even if this behaviour results in less clinical benefits for patients and society. This model has its maximal expression when the operation is based on a fee for service model, especially when there is no measurement and documentation of significant Clinical Outcomes (Benefits and Harms) and when there is no control over the number, distribution and quality of providers. Another important characteristic that has to be evaluated is if detailed Real World Clinical Outcomes are being measured, because absence of this type of measurement and information prevents a clear understanding of the benefits and harms being generated by the system, reduces transparency about performance and main objectives, and reveals a System that is more profit-oriented than patient oriented. There is an economic theory that says that the Market will arrive at its equilibrium in the case of free competition and no price control but in the case of Health Systems, if health maximization is not the main focus, the equilibrium that will be achieved is the financial equilibrium and not the equilibrium that ends up with a healthier society, as the financial focus may lead to giving up necessary services and clinical efficiency [7]. For a Health Care System to be patient-oriented it is essential to have information about relevant clinical outcomes like length of life and quality of life. As an example, to understand the impact of the number of CTs or MRIs that is done per 1,000 citizens of a population on significant clinical outcomes, this evaluation cannot be based only on the ratios. Without taking into consideration the clinical benefits and harms the discussion becomes ideological or emotional.

The interpretation of the impact of technologies on the level of health is complex because the analysis has to include many simultaneous variables that may interact among them, and we have to separate simple correlation from cause and effect.

All the countries make a decision about what is the main objective of their Health Care Systems, even without noticing, and this is reflected in how the Health Care System operates. Sometimes citizens and managers cannot see clearly the model of their countries, and because of this, some discussions and initiatives focused on reducing waste, improving clinical outcomes and improving the non-financial performance of Health Care Systems do not work. If discussions and actions are run and defined assuming that payers, like Health Maintenance Organizations, and providers will operate with the objective of maximizing the level of health and wellbeing of patients and society, but the real objective is to maximize revenues and

profitability, the System will never significantly improve its performance and will not achieve its projected social objectives. Lack of transparency about objectives and main goals is a problem because, without this level of honesty, the negative consequences of the choices and actions will never be approached in the best way to minimise the negative consequences that naturally occur with every choice.

One term that should be better understood and described is Value [43].

Payers, Providers, Industries and Patients will have different definitions and expectations when they talk about Value-Based Care. For Payers, Value may simply represent the capacity to match the available budget to the existing financial demands derived from the payments to the different players of the system. For Providers and Professionals, it is used interchangeably with Clinical Benefits, for Industries it can be just an argument to sell more of their products, and for Patients, families and society, it is to have access to any technology that gives them the perception that it will preserve or restore full physical and mental health.

Every time we talk about Value we have to take into consideration Costs, Clinical Outcomes and Efficiency [8–12]. By Efficiency, we mean having the ideal allocation of financial and human resources that will maximise clinical benefits, given the available budget. It is important to remember that we make choices all the time and even with the most appropriate and efficient decisions and actions, inevitably, losses will occur, because we do not have enough financial resources to give access to everything for everybody.

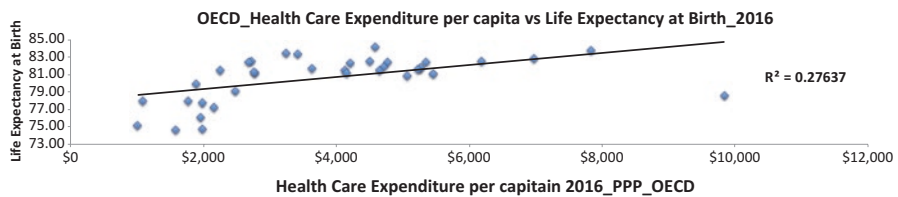
### 8.3 Financing of the Health Care System

A significant challenge that Health Care Systems and societies face is how to finance the incorporation and use of new technologies. Patients and families want to have immediate access to what they perceive as new, modern and innovative, even when there is no definitive or clear proof of the real benefit or superiority of a new treatment over old ones. There is a natural perception that more health care will end up with more health, but this is not necessarily true [13]. In most of the countries of the world, in the last decade, the increase of health care costs is higher than the growth of the economies [14]. This cost increase happens due to a continuous change of the age pyramid, with an increasing proportion of people older than 50 years old, unhealthy lifestyle, an increase in the access to and use of diagnostic procedures of image and lab tests, and a mindset that focuses more on treatment than prevention. The unitary cost of drugs, devices, and procedures is also contributing to a significant increase in health care costs above inflation and economic growth.

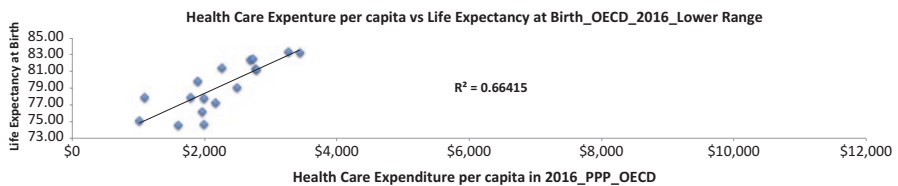
An important information is what is the correlation between the amount of money spent with Health Care and the level of Health of a Society. One way to try to understand this correlation is comparing what is spent per person per year with Health Care and Life Expectancy at Birth (LEB). When doing this comparison we have to use the expenditure in Health Care per capita. The use of the percentage of the global GDP (Gross Domestic Product) to compare Health Care spending of

countries and systems is not adequate, because it is a relative number and gives us no idea of the absolute amount that is being spent. As an example, assuming the use of 9% of the projected GDP for 2018 in Brazil in Health Care means that the Health Care Expenditure per person in 2018 will be US\$ 869 dollars, but 9% of the United States GDP allocated to Health Care would represent an expenditure of US\$ 5,500 dollars per person in 2018. [15, 16] It is not uncommon to see publications discussing how adequate is the Health Care Expenditure based on the per cent of GDP spent on Health Care. Another comparison we can use to evaluate the adequacy of Health Care Expenditure is the correlation between Health Care Expenditure and Infant Mortality. This comparison minimizes the problem of the lag between the time of investment and the time of clinical benefit.

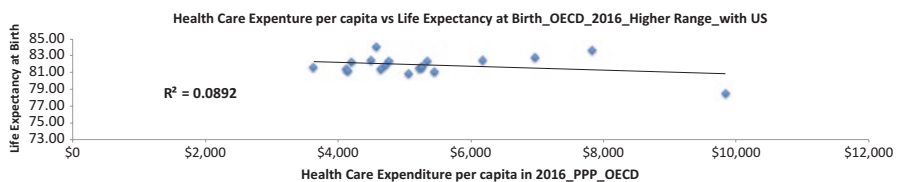
Using OECD data of 2016, Figs. 8.1, 8.2 and 8.3 show the linear correlation between Health Care Expenditure per capita and Life Expectancy at Birth. [17]



**Fig. 8.1** Correlation between the variation of Health Care Expenditure per capita per year and Life Expectancy at Birth in 2016 for the OECD countries (PPP adjusted)



**Fig. 8.2** Correlation between Health Care Expenditure per capita per year and Life Expectancy at Birth in 2016 for the OECD countries with Health Care Expenditure below US\$ 3500 dollars per capita per year (PPP adjusted)



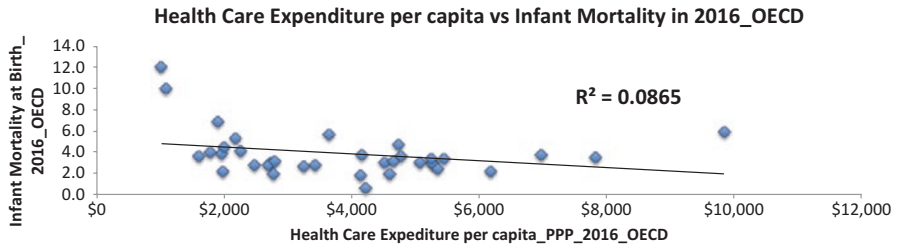
**Fig. 8.3** Correlation between Health Care Expenditure per capita per year and Life Expectancy at Birth in 2016 for the OECD countries with Health Care Expenditure above US\$ 3500 dollars per capita per year (PPP adjusted)

Figure 8.1 comprises all the OECD countries. The  $R^2$  depicted in the charts is the coefficient of determination (COD) and this number reflects how much of the variation in Life Expectancy at Birth can be explained by the variation in Health Care spending per capita [18, 19]. Based on this regression, for the whole OECD community, 27.6% of the variation in LEB can be explained by the variation in Health Care Expenditure per Capita (HEpC), but we can see that there is a subgroup of countries, with HEpC varying from US\$ 1,020 to US\$ 3,429 per capita where the variation in HEpC explains 66.45% of the variation in LEB. In the opposite direction, the countries with HEpC varying from US\$ 3,639 to US\$ 9,832, only 8.9% of LEB can be explained by the variation in HEpC. When we evaluate Infant Mortality in relation to HEpC, we have similar results to those obtained when comparing HEpC to LEB. This type of information about the efficiency of the allocated financial resources is critical for those who have to make decisions and define policies. It is natural for society and health care providers to see innovation as the most critical part of the Health Care System, but most of the time innovation represents an incremental improvement that has to be put into context when analyzing the efficiency of the whole system and defining what to offer to patients and society. Important to remember that innovation is simply a tool, how it is used is what defines how useful or not it will be. Changes and improvements in society happen because of people, not because of the innovations per se.

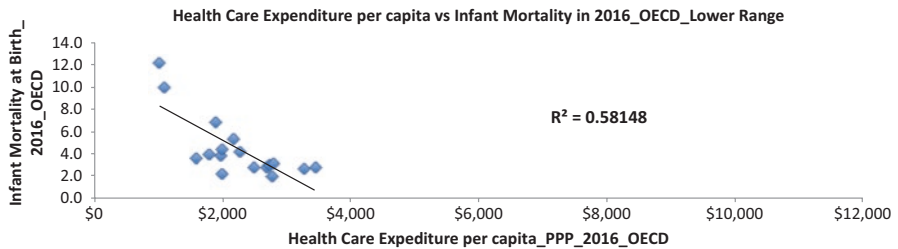
When defining how the country has to allocate financial resources, we also have to take into consideration the Social Determinants of Health and how they impact on the final level of health and quality of life of societies. By Social Determinants of Health, we mean education, sanitation, GDP per capita, among other variables. [20]

Figures 8.4, 8.5, 8.6 and 8.7 show the impact of HEpC on Infant Mortality for OECD countries.

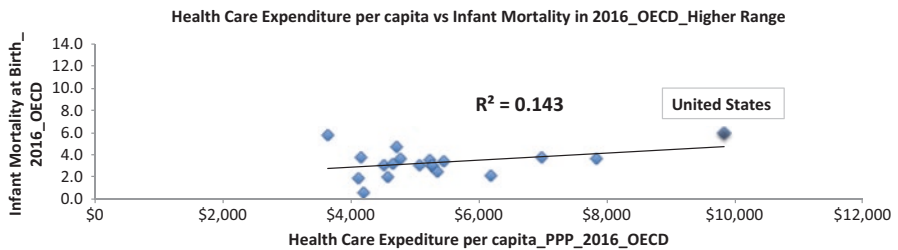
When we analyse all the OECD Countries in 2016 the COD is only 8.6% (Fig. 8.4), suggesting a very low impact of the variation of HEpC on Infant Mortality, but we can see that similar to the results obtained comparing HEpC and LEB, apparently, until a certain amount of expenditure, around US\$ 3,500 dollars, the volume of investment in Health Care per person has a significant effect on the measured outcome, explaining 58% of Infant Mortality (Fig. 8.5). This result also suggests that even for this range of HEpC there are other variables that will impact the final Clinical Outcomes. Figure 8.6 evaluates those countries with a HEpC above US\$ 3,500 and the regression appoints that the variation in expenditure does not lead to a significant improvement in the Infant Mortality Rate. It is interesting to observe that for this subgroup of countries there is a negative trend, with the trendline going up with the increase of HEpC. This happens because the United States is an outlier, with the highest HEpC and an Infant Mortality that is higher than the other countries included in the comparison. When we remove the United States from the analysis the COD is zero (Fig. 8.7).



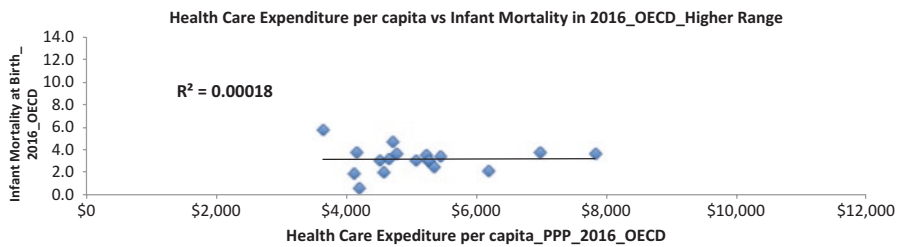
**Fig. 8.4** Correlation between Health Care Expenditure per capita per year and Infant Mortality in 2016 for the OECD countries (PPP adjusted)



**Fig. 8.5** Correlation between Health Care Expenditure per capita per year and Infant Mortality in 2016 for the OECD countries with Health Care Expenditure below US\$ 3500 dollars per capita per year (PPP adjusted)



**Fig. 8.6** Correlation between Health Care Expenditure per capita per year and Infant Mortality in 2016 for the OECD countries with Health Care Expenditure above US\$ 3500 dollars per capita per year, including the United States (PPP adjusted)



**Fig. 8.7** Correlation between Health Care Expenditure per capita per year and Infant Mortality in 2016 for the OECD countries with Expenditure above US\$ 3500 dollars per capita per year, excluding the United States (PPP adjusted)

## 8.4 Incorporation of Technologies

There are specific methods that are used to evaluate the value of new technologies and the information that is generated can be used to help make decisions about their incorporation.

Economic Evaluations always use the available or projected information about costs and outcomes to compare two or more interventions. The objective is to define what is the most efficient way to allocate scarce resources, based on explicit criteria.

Cost-Effectiveness Analysis is the term used to define the main technique that is used to describe the methodology that supports health care decisions, but this term may be used vaguely or be perceived differently by different groups like patients, providers, payers, industries and policymakers.

It is critical to know the Perspective of the study and understand the research methodology when reading an economic study. By Perspective we mean who is the decision maker. As an example, we can adopt a Societal or Payer's Perspective. This definition will define the data that will be used to determine the costs that will be evaluated and included in the study.

Cost-effectiveness, Cost-Utility and Cost-Benefit Analysis are different techniques that can be confused and are broadly termed Cost-Effectiveness.

Here we will concentrate on Cost-Effectiveness and Cost-Utility.

Table 8.1 shows the characteristics of the different economic studies [21].

The cost-effectiveness analysis takes into consideration the incremental costs and effects of one or more new interventions compared to a standard one. The comparator can be another new intervention, a standard treatment or no treatment at all. This calculation is called Incremental Cost-Effectiveness Ratio (ICER).

The ICER is calculated dividing the difference in costs by the difference in health outcome.

**Table 8.1** Types of Economic Studies

Measurement of costs and consequences in economic evaluations			
Type of study	Measurement/valuation of costs in both alternatives	Identification of consequences	Measurement/valuation of consequences
Cost-effectiveness analysis	Monetary units	Single effect of interest, common to both alternatives, but achieved to different degrees	Natural units (e.g. Overall survival, disability days saved, cholesterol reduction)
Cost-utility analysis	Monetary units	Single or multiple effects of interest, not necessarily common to both alternatives	Healthy years (Typically measured as Quality Adjusted Life Year (QALY))
Cost-benefit analysis	Monetary units	Single or multiple effects of interest, not necessarily common to both alternatives	Monetary units



The same rationale applies to diagnostic and therapeutic procedures, although the evaluation of diagnostic techniques is less common.

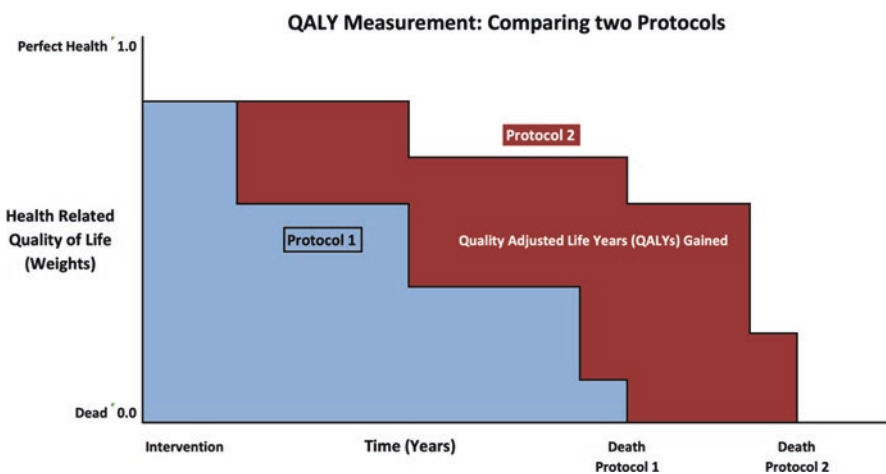
Table 8.2 shows an example of the ICER calculation. If we use Overall or Disease Free Survival as the outcome, measured in Years of Life, we will call it a Cost-Effectiveness Study, if we use Quality Adjusted Life Years (QALYs) as the outcome measure, we will call it a Cost-Utility Study. We will define that both Cost-Effectiveness and Cost-Utility studies will be considered Cost-Effectiveness Analyses.

QALY is a measure that gives weights to the different periods of time that are lived along the projected length of life. When using the QALY methodology it is necessary to value the different states of health, on an interval scale that varies from 0 to 1, with 1 being equal to Perfect Health and 0 equals dead. Figure 8.8 shows a comparison between two different scenarios, with and without the implementation of a Programme, and the gains in time and quality of life with the incorporation of the Programme can be seen. [22–24]

Most interventions involve multiple costs and different clinical consequences, that can be beneficial or harmful and ideally all this information has to be captured by the economic study. It is necessary to understand the level of uncertainty of the information about costs and outcomes because the information is obtained from a

**Table 8.2** ICER calculation example

ICER calculation	Standard treatment	New cancer drug	Incremental	ICER (per year of life saved)
Costs	10,000	55,000	45,000	112,500
Outcome (Overall survival in years)	1.5	1.9	0.4	



**Fig. 8.8** QALY measurement and comparison of two treatment protocols

sample of the population, the one that is included in the clinical studies. When interpreting Clinical Studies we also have to pay attention to the possibility of bias and confounding. Another important point is the external validity, especially in relation to costs. As countries may have different practices and costs, extrapolation of an economic study from one country to another has to be dealt with carefully. Ideally, whenever different clinical and cost realities exist, a new economic study has to be done based on local information.

The studies will also vary in relation to the type of costs that are measured. This definition will be based on the Perspective of the study [25].

There are two main Perspectives, the Societal Perspective and the Payer's Perspective. The main difference will reside on the types of costs that will be included or not in the economic evaluation, mainly loss of Productivity (Indirect Costs) and Out-of-Pocket expenditure.

Using a Payer's Perspective, like Public Health Care or Private Insurance Companies, Productivity Lost and out of pocket expenditures are not a problem and the focus will be on Direct Medical Costs. When the research moves to a Societal Perspective, both losses of Productivity and Out-of-Pocket payments have to be included. We also have to know what different countries define as Health Care Expenditures to understand how comparable systems are and to make any adjustment in the projected costs for the analysis to be adequate.

We have the following types of costs [26]:

1. Health Care Costs/Direct Medical Costs: they measure the resources consumed by the Health Care System to offer the preventive, diagnostic or therapeutic Programmes that are being evaluated in the economic study. This measurement takes into consideration the costs that are incurred along the time horizon that is defined in the economic model. Normally there is a projection of future costs and outcomes, what brings more uncertainty to the final ICER calculation.
2. Patient and Family/Direct non Medical Costs: This includes out-of-pocket expending and should also include the money spent to pay Private Health Care Insurance, combining items like premiums, deductible, copayment and coinsurance.
3. Indirect Costs: They measure the productivity losses of patients and families due to death or disability.

How to interpret the ICER?

The ICER is an index, that based on the comparison of two or more technologies defines a value that reflects the incremental clinical benefit that is obtained in relation to an incremental amount of money that is spent. The ICER index is subject to the choices of inputs that are used to calculate it. For the same technology being evaluated, the ICER will be different when different comparators, different perspectives and different outcomes are used. This is why it is critical to understand the methodology that is being used in the economic evaluation [27, 28].

Figure 8.9 shows the ICER formula, where C1 is the Cost of the New Technology being evaluated and C2 is the Comparator. The same applies to the Effects, or

Fig. 8.9 ICER calculation

$$ICER = \frac{C1 - C2}{E1 - E2}$$

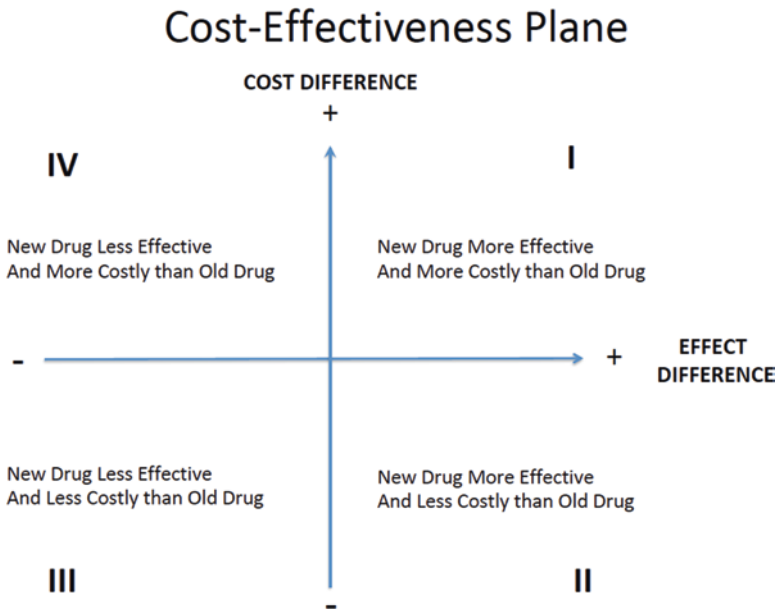


Fig. 8.10 Cost-effectiveness plane

Clinical Outcomes, where E1 reflects the Clinical Outcome that happens with the New Technology and E2 the Clinical Outcomes that exist with the Comparator.

Figure 8.10 shows the Incremental Cost-Effectiveness Plane, displaying the possible situations that can be faced when comparing two technologies. In this case, we are comparing a new treatment, a new drug, with an old one.

We can see four Quadrants. For two of them, the decision is straightforward. Quadrant II shows that the new drug is more effective and less costly and in this case the decision to incorporate is simple. Quadrant IV shows a situation where the new drug is more expensive and less effective, what leads to a very easy decision of not to incorporate the new drug. In Quadrant III, we have a new drug that is less effective and less costly. This type of situation demands a more detailed approach. Firstly we have to know how less costly and less effective is the new drug, because depending on the magnitude of the differences, it may be a wise choice to use the new drug to free the financial resources to be used in other prevention or therapeutic Programmes that may lead to significantly larger clinical benefits. But as the decision to move to a less effective technology is very difficult to be accepted by patients and providers, this type of movement almost never happens. This approach of

always taking into consideration the Opportunity Cost when making decisions, although absolutely critical, is rarely used, probably because it is difficult to have all the needed information about other technologies and because decisions are made based on individual economic studies that do not put into perspective the whole Health Care System. Again it is important to remember that depending on the comparator, differences between costs and effectiveness will vary for the technologies being compared, leading to different ICERs.

Quadrant I is the most common situation faced by those who have to make decisions about the incorporation of new technologies. In this case, the new drug or technology has higher costs and improved clinical benefits. In this situation, we also have to measure the variation in clinical benefits and compare to the variation in the measured costs and compare the obtained ICER to a value that is considered the reference to define if the new technology is cost-effective. This reference value is called Threshold.

The Threshold is a parameter that in theory will define if the new technology is cost-effective, or in other terms, valuable [29, 30]. In the UK the Threshold is accepted to vary from 20,000 to 30,000 pounds per QALY. For situations like Cancer and End of Life, the threshold can be above 30,000 per QALY. Recent research lead by Claxton has suggested it is around 13,000 pounds per QALY in the UK [31]. In the United States, most of the studies define the Threshold as 50,000 per year of life gained, but recent studies are moving this value to 100,000 or above [32]. For those countries where a defined value does not exist for the Threshold, one of the methodologies accepted to define is based on the World Health Organization WHO-CHOICE Project [33]. Under this approach that uses the DALY (Disability Adjusted Life Years), a measure that also takes into consideration time and quality of life. An intervention that costs less than three times the annual Gross Domestic Product per capita per DALY is considered cost-effective and in the case of costing less than once the GDP per capita per DALY it is considered highly cost-effective. The definition of the Threshold has to be put into a broader context, including affordability, budget impact and feasibility of implementation. Probably in many countries the Threshold should be projected based on previous incorporations and seen as an indicator to understand how Health Care Systems operate and not as a tool that is used to define if a new technology will be incorporated or not.

## 8.5 Clinical Outcomes and Health Improvement

How should physicians and other healthcare professionals behave, and how should they focus their study, training and operation to advance the efficiency of the Health Care System, to improve clinical results, to increase patient satisfaction and to stay as leaders of this system?

First critical point is to be capable of understanding the absolute clinical benefit of new technologies, how they add to, interact or replace old diagnostic and therapeutic procedures and how they apply to local practices.

Although the capacity to measure and understand the benefits and harms of new and old technologies sounds like something natural and straightforward, this is not the case.

In almost every country of the world, the existing financial resources are not large enough to provide the access of a whole population to all the old and new technologies that are available, and the volume of innovation and the availability of new technologies are increasing fast.

One significant point is that having access to technologies is not equal to receiving optimal care and achieving the best possible clinical outcomes. The only way to define if access translates into improved care is measuring clinical outcomes.

To maximise the efficiency of the Health Care Systems for patients and society, these Systems should be based on the principles of Universality, Integrality and Equity, but with the increasing difficulty to finance all the preventive, diagnostic and therapeutic technologies, efficiency has to be included as a 4th principle to highlight its critical importance [34]. We then come back to the need of high-quality information about costs and outcomes.

Another concept that has to be discussed is Evidence-Based Medicine (EBM) [35]. We cannot define that only Randomised Controlled Trials (RCT) and Meta-Analysis can be defined as EBM. Observational studies will be increasingly important to measure the clinical benefits and associated costs of new technologies, especially drugs. What is critical in a study is the quality of the methodology used and how adequate was the conduction of the study [36]. A well run Phase II study, with a good methodology, is better than a Randomized Controlled Trial that has a weak methodology, is biased, or is inefficiently conducted [37, 38]. As we increase fast the number of new diagnostic and therapeutic technologies and we move to a Personalized Medicine approach it will be almost impossible to have an RCT for all the drugs, devices or procedures in every possible clinical situation [39]. With the increasing number of drugs being developed for an escalating number of diseases that are restricted to a small number of patients, Real World Observational Studies will have to be used more frequently and together with RCTs will define the absolute and relative benefits of technologies, how they compare and when and how they should be incorporated and adopted.

RCTs have the risk of low external validity. In RCTs physicians, institutions and patients that participate in the studies come from specialized high volume institutions that may not reflect what happens in the community practice. Some studies also deal with procedures where a learning process exists and the performance of professionals may vary significantly from one practice to another. As an example, diseases like rectal cancer and prostate cancer, that demand a complex surgery and a highly skilled surgical team, need to have Real World outcomes measured from local smaller centres, to see if they match in terms of cure rates and complications the numbers that come from specialized high volume institutions.

When using data coming from RCTs to make decisions, we use the median value of a sample and we make decisions about treatment as if all the patients in a population were the “median patient” of the study [40]. We do not take into consideration the heterogeneity of the results that exist in the whole sample. We use numbers

based on populational studies to make decisions about individual patients. If we want to move to a Personalized Medicine approach, studies have to increase the capacity to understand what happens on an individual basis, generating information that will help make decisions for specific patients.

### ***8.5.1 Clinical Outcomes/Surrogate Markers***

This is another topic that we have to deal with.

Using the Patients' perspective, they do not have the same capacity to judge health benefits as they have to evaluate other things like foods, clothes, entertainment, TVs, cars. Health Care Managers and Providers do not give to society clear and precise information about the efficiency and performance of technologies, professionals and Institutions. Although it is necessary to understand and measure the patients' perception and satisfaction about their care, we cannot use patient satisfaction as a substitute of Clinical Outcomes, because this correlation is not perfect and studies with different methodologies show different results. [41]

Another important question is that the volume of information and access to it increases rapidly. Based on an IBM research, in 2018, the amount of health information is doubling every 3 years; by 2020 it is estimated to double every 73 days. [42] There is no guarantee that this information is high quality and can be trusted. This combination of high volume and low-quality information makes it impossible for a layperson to learn in a short period of time what is necessary to know to make the best decisions for him or for her. Patients will always depend on Health Care Professionals to have access to the best Health Care. What is important is that Health Care Professionals have an intense interaction with patients and society to understand their needs and preferences to use this information, in conjunction with his or her specialized knowledge, to choose the best use of diagnostic and therapeutic procedures for the patients they care for.

#### **Checklist for Planning, Designing, Implementing and Running an Efficient and Ever Improving Health Care System**

1. What are the Financial Resources and where do they come from? Financial Resources may come from the Government, from Private Health Insurance and from Out-of-Pocket and they require different strategies to optimize their allocation.
2. What are the health and health care needs of the population?
3. What are the Clinical Outcomes delivered by the current Health Care System?
4. How efficient is the current Health Care System and what are the possible improvements?
5. How to define cost-effectiveness and value, anchoring this definition and methodology to the available budget?
6. How to allocate the available financial resources, based on the different needs of the population in a way that we can maximize the total level of health of a society?

7. How to create an information system that gives the necessary information on costs, outcomes and efficiency on a real-time basis?
8. How to define and measure the indicators that will be used to evaluate the performance and evolution of the Health Care System?
9. How can Economic Studies help create an efficient Health Care Operation, that using the information that is continuously obtained and the available budget, is capable of making the necessary changes and adjustments that are required along the time to have a sustainable system that continuously improves its efficiency and the level of health of a society?
10. What is the best way to add digital and mobile resources and how to include information coming from these sources in economic evaluations? Examples are: how useful can be the incorporation of strategies like blockchain? How can we improve the utilization of Electronic Medical Records, turning them into a more friendly tool for health care providers and a more useful tool for patients and Health Care Systems?
11. How to use Social Media to generate information and to change behaviors? How can Economic Studies capture this effect?
12. How other Social Determinants of Health, like Education, Sanitation, Economic Situation (GDP per capita) and Security, are interacting with the Health Care System?

### Questions

What is Economics?

1. A Formal Science similar to mathematics, that is focused on complex calculations and modelling.
2. A Natural Science that studies biological factors of the Universe and tries to apply them to understand and manage how people live in the society.
3. A Social Science that studies how to make decisions and how to allocate scarce resources.
4. It is not a Science, it is one of the branches of Mathematics

Why taking opportunity costs into consideration is important?

1. Because the cost of health care is increasing very fast?
2. Because any choice that is made implies in giving up something, and understanding the possible losses is important to make decisions that maximise the use of resources.
3. Because any opportunity that is lost leads to financial losses.
4. Because when we do not take opportunity costs into consideration we lose the opportunity to negotiate better prices.

What should be measured to define the value of a new or old technology?

1. How much was spent to offer a diagnostic or therapeutic procedure.
2. Clinical Outcomes associated with the disease or system being studied.
3. The number of professionals involved in the care of the patients.
4. Both Costs and Outcomes.

When evaluating the Investment in Health Care, what are the variables that should be analysed?

1. Health Care Expenditure per capita, Inequality Index and Meaningful Clinical Outcomes.
2. Total Health Expenditure, without taking into consideration the Population.
3. The percentage of the Gross Domestic Product dedicated to Health Care.
4. How much is spent to offer inpatient care.

Which one of the sentences is correct?

1. There is always a perfect correlation between the amount of money spent on health care and the magnitude of the clinical outcome.
2. There is no correlation between the amount of money that is spent and the clinical outcome.
3. Health Care Expenditures is one of the variables that will impact on the level of health of a society, but there are other variables that can make a significant impact.
4. Improvements in Education and Economic Prosperity are not associated with advancements in the level of health of a society.

Which type of economic study does not follow an adequate methodology?

1. Cost-effectiveness analysis
2. Cost-benefit analysis
3. Cost of disease analysis
4. Cost-utility analysis.

When reading an economic study, what is critical to know to evaluate the methodology and to interpret the results?

1. The Institution where the study was done.
2. The researcher who is the leading the study.
3. The Perspective, the type of study and what types of costs and outcomes where measured.
4. If it was done by a public or private Institution.

What is the type of Outcome that is measured in Cost-Utility Studies?

1. Outcomes that are specific to each type of disease, like levels of cholesterol or A1c Hemoglobin.
2. Financial outcomes incurred by the patient and his or her family.
3. Healthy years, being QALYs the most frequently valuation.
4. The level of satisfaction with the care received by health care providers.

Which of the sentences is not correct?

1. The main Perspectives of an economic study are Societal and the Payer's perspectives.
2. Using a Societal Perspective, Indirect and out-of-pocket costs are included in the analysis.



3. The conclusions that come from a study that is done in one country can immediately be used to make decisions in other countries.
4. When projecting indirect costs we should include the loss of productivity that applies to patients and their families.

What are the different types of cost that are used in Economic Evaluations?

1. Direct costs, that represent what is spent by patients and families and Indirect Costs, that represent what is spent by Private Health Insurance Companies.
2. Indirect Costs, that represent what is spent by Families of Patients and Out-of-Pocket that represent what is spent by the Patients
3. Direct Non-Medical Costs, that represents what is spent by patients and families, including out-of-pocket, Direct Costs that represent the resources consumed by the Health Care System, and Indirect Costs that measure the loss of productivity of patients and families.
4. Direct Non-Medical Costs, that represents what is spent by patients and families, including out-of-pocket, and Indirect Costs, that measure the resources consumed by the Public System.

How is the Incremental Cost-Effectiveness Ratio Calculated?

1. Variation in Cost Divided by Variation in Effect (Clinical Outcome)
2. Clinical Outcome of the technology being evaluated Divided by the Clinical Outcome of the Comparator.
3. Variation in Clinical Outcome divided by Variation in Costs.
4. Cost of the New Technology divided by the Cost of the Comparator

Interpreting the Incremental Cost-Effectiveness Plane, we can say that:

1. Technologies that are in Quadrant I should be immediately incorporated.
2. Technologies that are in Quadrants II and IV should be immediately rejected.
3. Technologies in Quadrant III are those that are more costly and more effective.
4. Technologies in Quadrant I are those the demand a complex evaluation because they offer more clinical benefits but also consume additional financial resources to be incorporated.

Based on the WHO-CHOICE project, we can say about the cost-effectiveness of technologies.

1. Technologies that cost less than once the National annual GDP per capita are considered cost-effective.
2. Technologies that cost less than 5 times the National annual GDP per capita are considered cost-effective.
3. Technologies that cost less than 3 times the National annual GDP per capita are considered highly cost-effective.
4. Technologies that cost less than once the National annual GDP per capita are considered highly cost-effective.

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# **Part II**

## **Solid Tumors**

# Chapter 9

## Non-small Cell Lung Cancer



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**Abstract** Non-small cell lung cancer (NSCLC) is most common cause of cancer death in the world. Early detection, diagnosis and treatments are the essential strategies for increased overall survival of patients. Recently, staging of NSCLC is updated to 8th edition of TNM staging for NSCLC issued by the IASLC which affects to overall survival and treatment methods. This chapter include the incidence and risk factors of lung cancer, screening for lung cancer, diagnostic investigation, pathology, stage, and current treatment modalities in each stage of disease. There are many issues in term of multimodality treatments including surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy.

**Keywords** NSCLC · Diagnosis · Stage · Pathology · Treatment modalities

### Abbreviations

AATS	American Association for Thoracic Surgery
ACCP	American College of Chest Physicians
ACS	American Cancer Society
ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology

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BSC	Best Supportive Care
CCRT	Concurrent Chemoradiotherapy
CI	Confidence Interval
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
DFS	Disease-Free Survival
EBUS-NA	Endobronchial Ultrasound Needle Aspiration
EGFR	Epidermal Growth Factor Receptor
ESMO	European Society for Medical Oncology
FEV1	Forced Expiratory Volume in 1 second
IASLC	International Association Study of Lung Cancer
IV	Intravenous
LEC	Large Cell Carcinoma
LN	Lymph Node
LOS	Length of Hospital Stay
L-SND	Lobe-Specific Node Dissection
LUL	Left Upper Lobe
MLN	Mediastinal Lymph Node
MS	Median Survival
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small Cell Lung Cancer
OS	Overall Survival
PFS	Progression-Free Survival
QOL	Quality of Life
RCT	Randomized Controlled Trial
RML	Right Middle Lobe
RR	Response Rate
RT	Radiotherapy
RUL	Right Upper Lobe
SABR	Stereotactic Ablative Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SCC	Small Cell Carcinoma
SCRT	Sequential Chemoradiotherapy
SLND	Systematic Lymph Node Dissection
SLNS	Systematic Lymph Node Sampling
SQCC	Squamous Cell Carcinoma
TBNA	Transbronchial Needle Aspiration
TKI	Tyrosine Kinase Inhibitor
TTNA	Transthoracic Needle Aspiration
USPSTF	US Preventive Services Task Force
VATS	Video-assisted Thoracoscopic Surgery

## 9.1 Introduction

Non-small cell lung cancer (NSCLC) is most common cause of cancer death in the world. Early detection, diagnosis and treatments are the essential strategies for increased overall survival. Recently, staging of NSCLC is updated to 8th edition of TNM staging for NSCLC issued by IASLC. Moreover, multimodality treatments including surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy have been rapidly developed especially in immunotherapy era. This chapter will describe epidemiology, molecular mechanisms, diagnosis, and updated treatment strategies according to evidence-based medicine.

## 9.2 Epidemiology

### 9.2.1 Incidence and Prevalence

In 2017 in the United States of America, the estimated new cases of lung cancer were the second most common cancer both in men (prostate was first) and women (breast was first) which was 14% and 12% of all cancer respectively. However, the incidence rates trends to gradually decline, both in men and women [1]. In 40 European countries, lung cancer rates in men tend to have a stability or are slowly decreasing, but in women are still increasing [2]. In Australia, it is the fourth most common cancer both in men and women [3]. In Asian, it is the most common cancer in men, and third most common in women [4], however the incidence of lung cancer in China is highest compared to other areas [5]. In term of mortality rate, lung cancer was the most common cause of cancer death almost all area in the world in both gender. The incidence and mortality of lung cancer in each area was shown in Table 9.1.

**Table 9.1** Incidence of and mortality in each area; men and women

Regions	Incidence rate <sup>a</sup>		Mortality rate <sup>a</sup>	
	Men	Women	Men	Women
United States of America	75.0	53.5	57.8	37.0
European countries	68.3	21.6	33.3	14.6
Australia	55.8	34.1	44.6	24.2
Asia	32.4	13.1	28.1	11.0
China	509.3	224.0	432.4	177.8

<sup>a</sup>rates are expressed per 100,000 people

## 9.2.2 Risk Factors

Risk factors of lung cancer are multifactorial including occupational or domestic substances exposure [6–10], smoking [11–13], chronic lung disease [9] [14, 15], radioactive exposure [16, 17], family history [18], HIV infection [19], and genetic factor [20–27]. The odd ratios (OR) and 95% CI of risk factors of lung cancer were demonstrated in Table 9.2.

**Table 9.2** Risk factors associated with lung cancer

Risk factors	Odd ratios	95% Confidence interval
Exposure status of tobacco and asbestos		
Men		
Never-smoker and asbestos	1.26	1.04–1.53
Ever smoker and never asbestos	9.23	8.13–10.5
Ever smoker and asbestos	11.9	10.5–13.6
Women		
Never-smoker and asbestos	1.00	0.78–1.29
Ever smoker and never asbestos	4.57	4.08–5.12
Ever smoker and asbestos	6.26	5.14–7.62
Passive smoking	1.31	1.17–1.47
Smoking opium	3.10	1.20–8.10
Heavy smoking cigarette and opium	35.0	11.4–107.9
Chronic lung disease		
COPD or interstitial lung disease		
FEV1/FVC < 70%	7.17	4.03–12.74
%VC < 80%	4.73	2.00–11.17
LAA score $\geq$ 1	3.63	2.24–5.89
Fibrosis score $\geq$ 1	5.10	2.82–9.24
GGA score $\geq$ 1	2.71	1.52–4.81
Substance related occupational exposure		
Welding activity		
Regular welder	1.70	1.10–2.50
Gas welding	2.00	1.20–3.30
Arsenic (drinking water, >800 $\mu$ g/L)	5.24	3.05–9.00
Chromium	2.40	1.20–4.80
Cadmium	4.70	1.50–14.30
Nickel	2.50	1.30–4.70
Radioactive substance exposure		
Radon (> 200 Bq/m <sup>3</sup> )	2.42	1.45–4.06
Family history of lung cancer		
Occupational exposure to organic dust	1.12	1.02–1.24
Substance from cooking		
Domestic cooking fuel		

(continued)



**Table 9.2** (continued)

Risk factors	Odd ratios	95% Confidence interval
Biomass fuel	5.33	1.70–16.70
Mixed fuels	3.04	1.10–8.38
Genetic polymorphisms		
Rs2736100 (C allele)	1.51	1.18–1.93
Rs1042522 (Arg72Pro)	1.14	1.10–1.19
Rs1800470 polymorphism	1.36	1.06–1.74
TT genotype of NQO1 rs1800566	1.78	1.14–2.79
Genotype of N-acetyltransferase 2 (NAT2)	10.90	1.75–67.5
HIV infection	1.70*	1.5–1.9
Heterozygous p.I171V mutation of the NBN gene	7.76	3.68–16.36
VEGF (vascular endothelial growth factor) rs699947		
In all race	1.76	1.10–2.81
In Asian	3.00	1.51–5.95
Complement factor H polymorphism rs1061170	2.51	1.07–5.90
Hyposia-inducible factor (HIF)		
AA genotype of HIF2A rs13419896	0.54	0.30–0.99
CC genotype of VEGFA rs833061	0.42	0.24–0.75

*COPD* Chronic obstructive pulmonary disease, *LAA* Low attenuation area, *GGA* Ground glass attenuation

LAA was assessed using Goddard's scoring system, GAA and fibrosis scores were assessed using Kazzerooni's scoring system

\*Reported as risk ratio

### 9.2.3 Molecular Mechanisms

For adenocarcinoma, cancer Genome Atlas (TCGA) has published the comprehensive molecular profiling of 230 lung adenocarcinomas in 2014. High rates of somatic mutations detected by whole-exome sequencing were reported (means: 8.87 per megabase) including 18 statistically significant genetic mutations (Table 9.3) [28]. Driver genetic alterations in lung adenocarcinomas differ between Caucasians and Asians, and depend on smoking status [29]. *EGFR*-mutated adenocarcinomas are characterized by East-Asian ethnicity, female gender, and non/light-smoking history [30]. While *KRAS*-mutated adenocarcinomas are frequently detected in Caucasians and smokers. *EGFR*-mutated adenocarcinomas typically show hobnail cell type with nuclear TTF-1 immunostaining expression. Higher frequency of *EGFR* mutation is observed in adenocarcinomas with a micropapillary pattern than adenocarcinomas without this pattern [31, 32]. Several fusion or rearranged genes are reported in lung adenocarcinomas and considered oncogenic drivers; *ALK*-rearranged (5–7%), *ROS*-rearranged (1%), and *RET*-arranged (1%) [33–35]. Additionally, 75% of lung adenocarcinomas also have genetic alterations that promote the RTK/RAS/RAF signaling pathway including *KRAS* (32%) mutation, *EGFR* (11%) mutation, *BRAF* (7%) mutation, and *MET* exon 14 skipping (4.3%). This information widened the potential therapeutic targets for the treatment of lung

**Table 9.3** Somatic mutations in lung adenocarcinoma

Somatic mutations	%
<i>TP53</i>	46
<i>KRAS</i>	33
<i>KEAP1</i>	17
<i>STK11</i>	17
<i>EGFR</i>	14
<i>NF1</i>	11
<i>BRAF</i>	10
<i>SETD2</i>	9
<i>RBM10</i>	8
<i>MGA</i>	8
<i>MET</i>	7
<i>ARID1A</i>	7
<i>PIK3CA</i>	7
<i>SMARCA4</i>	6
<i>RBI</i>	4
<i>CDKN2A</i>	4
<i>U2AF1</i>	3
<i>RIT1</i>	2

Data from Cancer Genome Atlas Research Network Nature [28]

adenocarcinomas as well [36]. TCGA provides new transcriptional molecular subtypes of lung adenocarcinomas; the terminal respiratory unit (TRU, formerly bronchioid), the proximal-inflammatory (PI, formerly squamoid), and the proximal-proliferative (PP, formerly magnoid) [37]. The TRU subtype is a majority of the *EGFR*-mutated adenocarcinomas. The PI subtype typically has solid morphology and co-mutation of *TP53* and *NF1*. The PP subtype is enriched for *KRAS* mutation and *STK11* inactivation [28]. DNA methylation profiling classifies lung adenocarcinomas into three subtypes; CpG island methylator phenotype (CIMP)-high which enriched for *MYC* overexpression, CIMP-intermediate, and CIMP-low. Protein profiling divides lung adenocarcinomas into six subtypes that partially overlapped with transcriptional subtypes [28].

Squamous cell carcinomas are characterized by complex genomic alterations due to the history of heavy smoking. TCGA identifies 11 statistically significant genetic mutations; *TP53* (most common, 90%), *CDKN2A*, *PTEN*, *PIK3CA*, *KEAP1*, *MLL2*, *HLA-A*, *NFE2L2*, *NOTCH1*, *RBI*, and *PDYN*. The mRNA profiling divides SQCC into four subtypes; classical, basal, secretory, and primitive. The MicroRNA profiling divides SQCC into four subtypes which roughly overlapped with the mRNA subtypes. DNA methylation profiling also divides SQCC into four subtypes (methylation clusters 1–4) [36].

### 9.3 Lung Cancer Screening

The National Lung Screening Trial (NLST) enrolled 53,000 current or former heavy smokers to assess the risk and benefits of low-dose CT scans compared with CXR for detecting lung cancer and found that screening using low-dose CT in individuals with high-risk factors (either current or former smokers with a  $\geq 30$  pack-year smoking history (former smokers had quit up to 15 years before enrollment), age 55–74 years, and no evidence of lung cancer) decreased the mortality rate by 20% [38]. The NCCN, ACS, USPSTF, ACCP, ASCO and other organizations recommend lung cancer screening using low-dose CT for select high-risk patients as shown in Table 9.4.

**Table 9.4** Inclusion criteria for low-dose computed tomography screening for lung cancer

Organization	Age (year)	Smoking History (Pack-years) <sup>a</sup>	Years since quitting smoking	Other
NCCN				–
Group1	55–74	$\geq 30$	< 15	–
Group2	$\geq 50$	$\geq 20$		At least 1 additional risk factor <sup>b</sup> other than second-hand smoke
ACCP, ACS, ASCO and ESMO	55–74	$\geq 30$	< 15	–
AATS				
Tier 1	55–79	$\geq 30$	–	
Tier 2	$\geq 50$	$\geq 20$	–	Additional cumulative risk <sup>c</sup> $\geq 5\%$ of developing lung cancer within 5 years
CMS	55–77	$\geq 30$	<15	–
USPSTF	55–80	$\geq 30$	<15	–

NCCN National Comprehensive Cancer Network, ACCP American College of Chest Physicians, ACS American Cancer Society, ASCO American Society of Clinical Oncology, ESMO European Society for Medical Oncology, AATS American Association for Thoracic Surgery, CMS centers for medicare & Medicaid services, USPSTF US Preventive Services Task Force

<sup>a</sup>Pack-year calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked (20 cigarettes = 1 pack)

<sup>b</sup>Additional risk factors of lung cancer include (1) COPD or pulmonary fibrosis, (2) A parent, sibling, or child with lung cancer, (3) Having had certain cancers, (4) Major contact with radon, asbestos, arsenic, beryllium, cadmium, chromium, nickel, coal smoke, soot, silica, or diesel fumes

<sup>c</sup>The cumulative risk of developing lung cancer include (1) COPD with % predicted FEV1  $\leq 70\%$ , (2) environmental and occupational exposures, (3) any prior cancer or thoracic radiation, (4) a genetic or family history

## 9.4 Clinical Presentation

The clinical presentation of lung cancer patients includes cough (8–75%), weight loss (0–68%), dyspnea (3–60%), chest pain (20–49%), hemoptysis (6–35%), bone pain (6–25%), weakness (0–10%), dysphagia (0–2%) [39] depending on the location of tumor (local effects; peripheral lesion (asymptomatic or chest pain) or central lesion (chronic bronchitis, obstructive pneumonitis, atelectasis, or hemoptysis)), sites of metastasis (brain; headache, alteration of consciousness), bone (bone pain at rest), liver (abdominal pain), or paraneoplastic syndrome (such as hypercalcemia, acanthosis nigricans or hypertrophic osteoarthropathy). More than three-fourths of patients have symptoms and more than 70% present with advanced disease [39]. In early stage or resectable cases, patients usually presented with hemoptysis (42.3%), chronic cough (44%), some are asymptomatic (35.7%) [40]. Other less common clinical presentations were reported such as cardiac tamponade [41], sternal mass [42], choroidal metastasis [43], upper gastrointestinal bleeding [44], rhinophyma [45] and adrenal insufficiency [46].

## 9.5 Diagnosis and Staging

### 9.5.1 *Non-invasive Diagnostic Tools*

The imaging modalities used for investigation in NSCLC consist of chest radiography (CXR), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and integrated PET/CT. The objectives for imaging include as follow: (1) Staging of the disease; (2) Evaluate the primary tumor, search for the lymphadenopathy and identify the metastatic lesions both intra and extra-thoracic lesion; (3) Guide for tissue sampling; (4) Plan for the specific treatment; and (5) Evaluate the tumor response after treatment and identify some complications during or after treatment. CXR remains the primary modality radiographic assessment of NSCLC due to its commonly availability, relatively affordable cost, non-invasive, and lower radiation exposure. The limitation of CXR to detect lung cancer include; (1) Since the CXR is fundamentally a 2D depiction of a 3D thoracic structure, the overlapping chest wall of mediastinal structures may obscure the lung cancers; (2) a very small nodule cannot be detected because of low density, especially non-calcified nodules <7 mm that may never be visualized on CXR. The false positive rate for detection pulmonary nodule by CXR is ranging from 19–72% [47]; and (3) CXR has insufficient sensitivity for determining MLN metastases, mediastinal, pleura and chest wall involvement [48].

Intravenous contrast-CT scan of the thorax including upper abdomen (beginning from the supraclavicular region down to the adrenal glands) is now the imaging modality of choice for evaluating the patients with NSCLC and is performed in nearly all patients [48], while CT scans of the brain and abdomen are performed in some patients to identify metastatic disease. The contrast material facilitates the vascular or other organ involvement, characterizes the tumor and lymphadenopathy

and differentiates the vascular and non-vascular structures. The benefits of CT scan include accurate measurement of the tumor size, location, adjacent organ invasion, presence or absence of separate tumor nodules, mediastinal and hilar LN and other associated findings such as pleural effusion, pericardial effusion, bony chest wall destruction, atelectasis or obstructive pneumonitis, and distant organ metastasis.

There are some disadvantages for CT scans included; 1) the radiation dose of the CT scan is intensely higher (7–8 mSv) than that of the CXR [49]. Radiation exposure that exceeds 50–100 mSv may increase the risk of cancer development; however, the actual risk is still doubtful [50]; 2) the risk of contrast induced nephropathy (CIN) defined as a sudden worsening of renal function, > 25% increase in serum creatinine or 0.5 mg/dL (44  $\mu$ mol/L) increase in absolute value that occurs 48–72 hours after IV contrast material administration without other demonstrable causes [51]. There is very low risk for CIN if patients have eGFR >60 mL/min and specific prophylaxis or follow up is not required for these patient, except for hydration. For the patients who have eGFR <60 mL/min are considered at some risk for CIN. These patients should avoid dehydration, minimize contrast medium volume, avoid repeat contrast studies within 24–48 hours, use low or iso-osmolar non-ionic contrast medium, or consider alternate non-contrast imaging studies.

MRI is not an imaging of choice for evaluation the lung cancer because the lung parenchyma which mostly contains air has extremely low proton density and signal intensity, resulting in invisible signal on MRI and the continuous movement of the thoracic organs from the respiration and cardiac pulsation is also one principal problem for MRI. For lung cancer, MRI is better than CT to evaluate the mediastinal, pleural, chest wall, spinal, brachial plexus or vascular invasion, especially in the superior sulcus tumor [52]. MRI can also play an important role in differentiation between the tumor and adjacent consolidation, fibrosis or atelectasis [52].

PET scan using glucose bound with  $^{18}\text{F}$  to produce the 2-deoxy-2- $^{18}\text{F}$  fluoro-D-glucose ( $^{18}\text{F}$ -FDG) is the most frequent radionuclide using in the thoracic oncology because the cancer cells have more metabolic activity of the glucose as compared with the normal cells [52]. PET images alone may be impossible to correctly localize the area of increased uptake due to poor anatomic details; integrated PET/CT plays an important role in precise coregistration between the anatomical and functional images by achieving a PET and a CT study on the same scanner. The overall sensitivity and specificity of information provided by an integrated PET/CT is better than that of the PET or CT alone [52, 53]. Furthermore, the integrated PET/CT has a good differentiation between the malignant tumors which show increased FDG uptake and the benign conditions such as obstructive atelectatic lung or scar which reveal normal or decreased FDG uptake [54]. The SUV is a semiquantitative assessment ratio of the metabolic uptake which is calculated by using the amount of radio-tracer activity in a tissue per unit of volume and divides it by a normalizing factor [54, 55]. The normal tissues typically have an SUV ranging from 0.5–2.5 while the malignant tumors have an SUV of larger than 2.5 [54, 55]. The diagnostic index of CT or PET-CT for staging mediastinum was showed in Table 9.5. Integrated PET/CT is the most excellent noninvasive technique for nodal metastatic detection which shows accuracy approximately 78% [56, 57]. However, PET has a good negative predictive value but poor positive predictive value [58]; therefore tissue pathology to confirm the diagnosis is needed whenever positive from PET/CT.

**Table 9.5** Diagnostic procedures and their diagnostic index for staging of the mediastinum in patients with lung cancer

Procedures	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<b>Non-invasive techniques</b>				
CT scan	55	81	58	83
PET scan	80	88	75	91
PET-CT scan <sup>a</sup>	62	90	63	90
<b>Invasive techniques</b>				
<i>Needle techniques</i>				
TTNA	94	100	100	–
TBNA	78–87.8	98.7–100	99.1–100	77–82.5
EBUS-NA or EUS	80–91	98.5–100	100	86–91
<i>Surgical techniques</i>				
Mediastinoscope	78	100	100	91
VAM	89–96	100	100	92–99.6
Anterior mediastinotomy (for LN station 5,6)	71	100	100	91
Extended cervical mediastinoscopy (for LN station 5,6)	71	100	100	91
VATS	99	100	100	96

TTNA transthoracic needle aspiration, TBNA transbronchial needle aspiration, EBUS-NA endoscopic bronchial ultrasound and needle aspiration, VAM video-assisted mediastinoscope, PET/CT positron emission tomography/computed tomography, PPV positive predictive value, VATS video-assisted thoroscopic surgery, LN lymph node, NPV negative predictive value

Data from Silverstri et al. [154], Zielinski et al. [155], Labarca et al. [156]

<sup>a</sup>The false positive of the integrated PET/CT can be found in the infectious or inflammatory process while false negative may be found in minimally invasive adenocarcinoma (MIA), mucinous adenocarcinoma or carcinoid tumor, resulting in false negative study

### 9.5.2 Invasive Diagnostic Tools

Invasive techniques are subdivided into two methods; surgical techniques and needle techniques. Surgical techniques include mediastinoscopy (approach to mediastinal LN station 1, 2R, 2 L, 4R, 4 L, and 7), video-assisted mediastinoscopy, anterior mediastinotomy and extended cervical mediastinoscopy (for LN station 5,6) and VATS. The needle techniques include TTNA, TBNA and EBUS-NA. The diagnostic index of these technique was shown in Table 9.3. The chosen techniques for tumor staging depends on the location of the tumor, mediastinal LN and availability of diagnostic tools.

NCCN guideline 2018 summarized that patients suspected to have lung cancer, PET/CT scan should be performed in all cases. In clinical stage IA (peripheral T1abc, N0) pathologic mediastinal LN should be evaluated even if CT or PET negative in solid tumors >1 cm or purely non-solid tumors >3 cm. In clinical Stages

IB-IV NSCLC, MRI or CT brain should be performed if PET scan is not available and pathologic mediastinal LN must be evaluated. All patients with mediastinal LN positive from PET or CT scan, the invasive staging is recommended. In patients with high suspicion of N2,3 involvement, a needle technique should be performed first.

### ***9.5.3 Stage of Disease***

The IASLC has proposed the eighth edition of the TNM classification for Lung cancer since 2016 (Table 9.6) [59] and complete validation on 2017. The IASLC defined 7 zones (14 stations) of LN as shown in Fig. 9.1.

## **9.6 Pathology**

The pathologic classification of lung cancer has been revised and published as the 2015 WHO classification (Table 9.7) [60]. Non-small cell lung carcinoma (NSCLC) is categorized into adenocarcinoma, squamous cell carcinoma and large cell carcinoma.

### ***9.6.1 Adenocarcinoma***

Pulmonary adenocarcinomas are defined as a malignant epithelial tumor with an acinar/tubular structure or mucin production.

#### **9.6.1.1 Gross Pathology**

Pulmonary adenocarcinomas are firm, gray-tan with ill-defined borders with variable amounts of necrosis. Most of them present with one of six macroscopic growth patterns; (1) peripheral mass with fibrosis retracting the covering pleura; (2) central or endobronchial growth; (3) pneumonia-like consolidation; (4) diffuse visceral pleural thickening, simulating mesothelioma; (5) adenocarcinoma develops in the background of underlying fibrosis; and (6) diffuse bilateral lung disease [61].

**Table 9.6** The eighth edition of TNM classification for lung cancer proposed by IASLC [59]

<b>T – primary tumor</b>		
Tx		Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1		Tumor $\leq 3$ cm surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) <sup>a</sup>
	T1a(mi)	Minimally invasive adenocarcinoma <sup>b</sup>
	T1a	Tumor $\leq 1$ cm <sup>a</sup>
	T1b	Tumor $> 1$ cm but $\leq 2$ cm <sup>a</sup>
	T1c	Tumor $> 2$ cm but $\leq 3$ cm <sup>a</sup>
T2		Tumor $> 3$ cm but $\leq 5$ cm or tumor with any of the following features <sup>c</sup> :
		- involves main bronchus regardless of distance from the carina but without involvement of the carina
		- invades visceral pleura
		- associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
	T2a	Tumor $> 3$ cm but $\leq 4$ cm
	T2b	Tumor $> 4$ cm but $\leq 5$ cm
T3		Tumor $> 5$ cm but $\leq 7$ cm or associated with separate tumor nodule(s) in the <b>same lobe</b> as the primary tumor or directly invades any of the following structures:
		Chest wall (including the parietal pleura and superior sulcus tumors)
		Phrenic nerve
		Parietal pericardium
T4		Tumor $> 7$ cm or associated with separate tumor nodule(s) in a <b>different ipsilateral lobe</b> than that of the primary tumor or invades any of the following structures: Diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
<b>N: Regional lymph node involvement</b>		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

(continued)



**Table 9.6** (continued)

<b>M: Distant metastasis</b>							
M0		No distant metastasis					
M1		Distant metastasis present					
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion <sup>c</sup>					
	M1b	Single extrathoracic metastasis <sup>d</sup>					
	M1c	Multiple extrathoracic metastases in one or more organs					
<b>Stage</b>	T	N	M	<b>Stage</b>	T	N	M
Occult carcinoma	Tx	N0	M0	IIIB	T1a	N3	M0
0	Tis	N0	M0		T1b	N3	M0
IA1	T1a(mi)	N0	M0		T1c	N3	M0
	T1a	N0	M0		T2a	N3	M0
IA2	T1b	N0	M0		T2b	N3	M0
	T1c	N0	M0		T3	N2	M0
IA3	T1c	N0	M0		T4	N2	M0
IB	T2a	N0	M0	IIIC	T3	N3	M0
IIA	T2b	N0	M0		T4	N3	M0
IIB	T1a	N1	M0	IVA	Any T	Any N	M1a
	T1b	N1	M0		Any T	Any N	M1b
	T1c	N1	M0	IVB	Any T	Any N	M1c
	T2a	N1	M0	<b>A sub-classification of pleural invasion was divided into 4 categories:</b> <b>PL0</b> = tumor within the subpleural lung parenchyma; <b>PL1</b> = tumor invades beyond the elastic layer; <b>PL2</b> = tumor invades to the pleural surface; <b>PL3</b> = tumor invades into any component of the parietal pleura (PL1 or PL2 = T2a, visceral pleural invasion, PL3 = T3, parietal pleural invasion)			
	T2b	N1	M0				
	T3	N0	M0				
IIIA	T1a	N2	M0				
	T1b	N2	M0				
	T1c	N2	M0				
	T2a	N2	M0				
	T2b	N2	M0				
	T3	N1	M0				
	T4	N0	M0				
	T4	N1	M0				
<b>R classification</b>							
Rx	Presence of residual tumor cannot be assessed						
R0	Complete resection						
	Resection margins confirmed to be clear on microscopy						
	Six nodes/nodal stations removed/sampled for histological examination						

(continued)

**Table 9.6** (continued)

	These should include 3 nodes/stations from the mediastinum (at least at station 7 (subcarinal node), and 3 nodes/stations from the hilum or other N1 locations)
R0(un)	Uncertain resection Resection margins confirmed to be clear on microscopy but nodal assessment has less than the number of nodes/stations recommended for complete resection, or the highest mediastinal node Removed/sampled is positive
R1	R1 (cy+) The requirements for R0 have been met, but pleural lavage cytology (PLC) is positive for malignant cells. R1(is) The requirements for R0 have been met, but <i>in situ</i> carcinoma is found at the bronchial resection margin. R1 microscopic incomplete resection Microscopic evidence of residual disease at resection margin, extracapsular extension at margins of resected nodes, or positive cytology of pleural/pericardial effusion(R1cy+)
R2	Macroscopic incomplete resection Macroscopic evidence of residual disease at resection margins, extracapsular extension at margins of resected nodes, positive nodes not resected at surgery, or pleural/pericardial nodules.

**Note:** Tumor was measured in **greatest dimension**

<sup>a</sup>The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a

<sup>b</sup>Solitary adenocarcinoma,  $\leq 3$  cm with a predominately lepidic pattern and  $\leq 5$  mm invasion in any one focus

<sup>c</sup>Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor

<sup>d</sup>This includes involvement of a single distant (nonregional) lymph node

<sup>e</sup>T2 tumors with these features are classified as T2a if  $\leq 4$  cm or if size cannot be determined, and T2b if  $>4$  cm but  $\leq 5$  cm

### 9.6.1.2 Histopathology

This entity is classified based on the extent of invasion into adenocarcinoma in situ (AIS, preinvasive lesion), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma [36]. The diagnostic criteria for AIS and MIA are described in Table 9.8. Invasive adenocarcinoma is classified by single predominant patterns: lepidic, papillary, acinar, micropapillary and solid (Fig. 9.2).

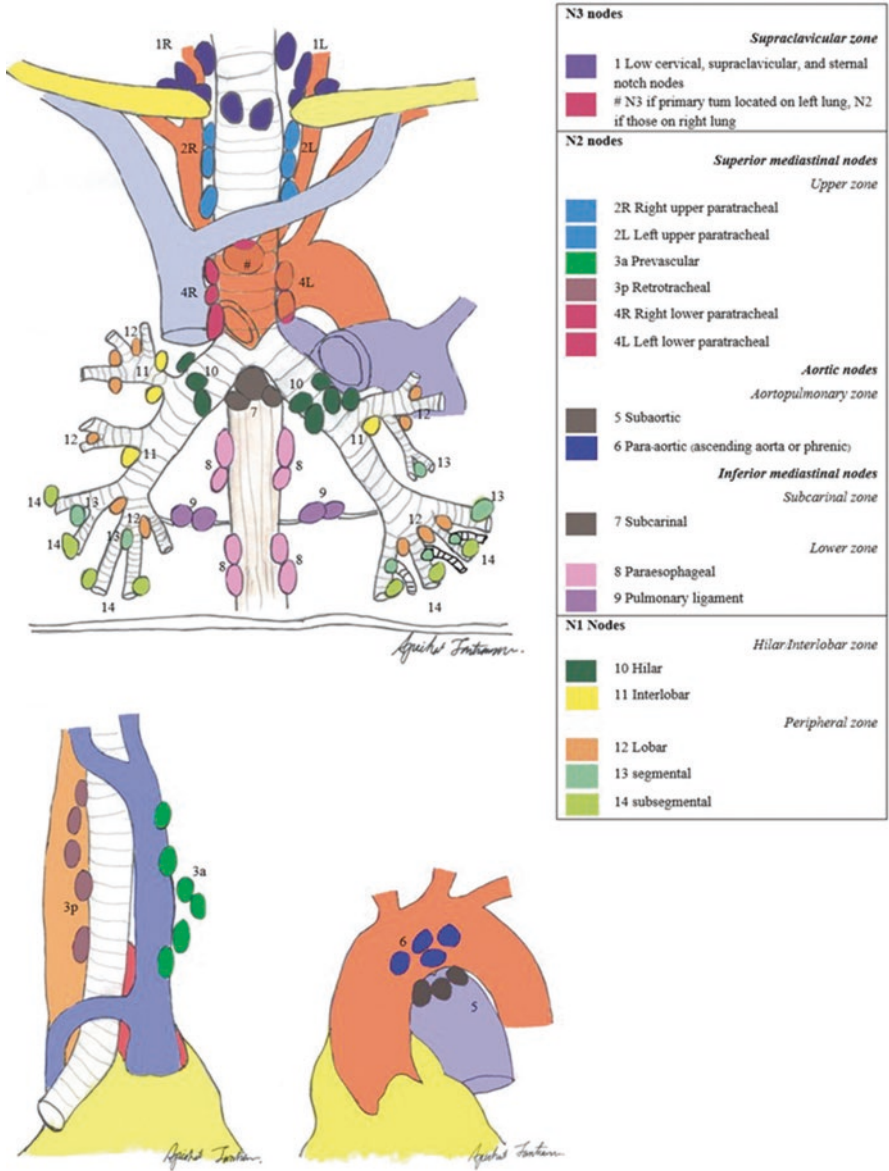


Fig. 9.1 Lymph node mapping according to the IASLC

**Table 9.7** 2015 WHO classification of major NSCLC

Cell type	Cell type
Adenocarcinoma	Squamous cell carcinoma
Lepidic adenocarcinoma	Keratinizing squamous cell carcinoma
Acinar adenocarcinoma	Nonkeratinizing squamous cell carcinoma
Papillary adenocarcinoma	Basaloid squamous cell carcinoma
Micropapillary adenocarcinoma	Preinvasive lesion
Solid adenocarcinoma	Squamous cell carcinoma in situ
Invasive mucinous adenocarcinoma	Large cell carcinoma
Mixed invasive mucinous and nonmucinous	
Adenocarcinoma	
Colloid adenocarcinoma	
Fetal adenocarcinoma	
Enteric adenocarcinoma	
Minimally invasive adenocarcinoma	
Nonmucinous	
Mucinous	
Preinvasive lesions	
Atypical adenomatous hyperplasia	
Adenocarcinoma in situ	
Nonmucinous	
Mucinous	

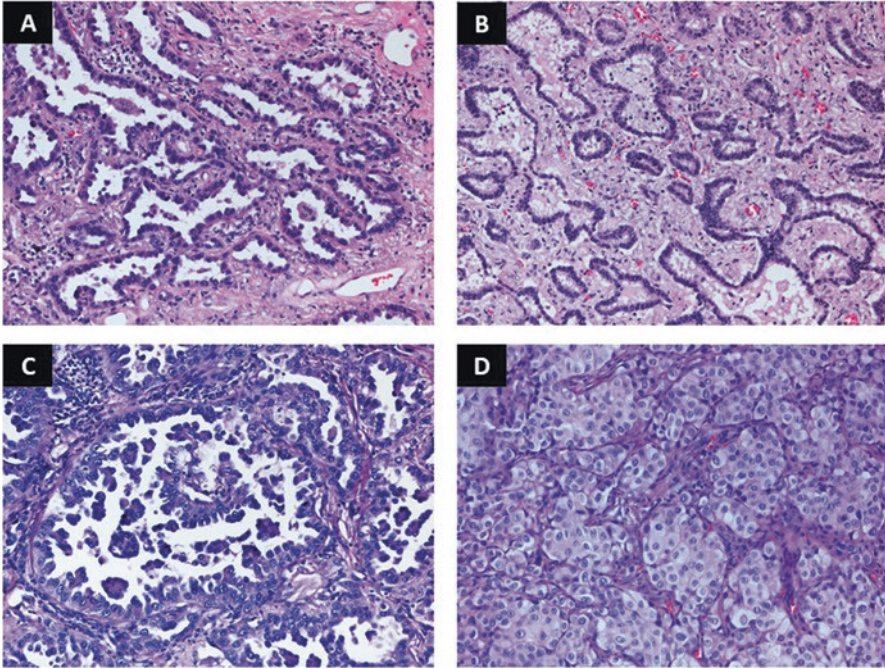
NSCLC Non-small cell lung carcinoma

Modified from Travis WD et al. [29]

**Table 9.8** Diagnostic criteria for adenocarcinoma in situ versus minimally invasive adenocarcinoma

Adenocarcinoma in situ (AIS)	Minimally invasive adenocarcinoma (MIA)
A small tumor ≤3 cm	A small tumor ≤3 cm
A solitary adenocarcinoma	A solitary adenocarcinoma
Pure lepidic growth	Predominantly lepidic growth
Cell type mostly nonmucinous type, but rarely may be mucinous	Cell type mostly nonmucinous type, but rarely may be mucinous
No pattern of invasive adenocarcinoma	Invasive component to be measured includes
No stromal, vascular or pleural invasion	Any histologic subtype other than a
No spread through air spaces	Lepidic pattern
	Tumor cells infiltrating myofibroblastic stroma
	MIA diagnosis is excluded if the tumor
	Invades lymphatic, blood vessels, air spaces or pleura
	Contains tumor necrosis
	Spreads through air spaces

Modified from Travis WD et al. [29]



**Fig. 9.2** Histologic subtypes of Adenocarcinoma. (a) Lepidic pattern is described as neoplastic cells lining the alveoli without architectural disruption or complexity. (b) Acinar pattern is defined by glandular formation of variable size and shape. (c) Micropapillary pattern is composed of small epithelial projections or tufting without fibrovascular cores. Whenever this pattern appears within any airspace structures (lepidic or acinar), the tumor should be classified as a micropapillary pattern. (d) Solid pattern is characterized by solid sheets and nests of tumor cells without definite glandular structures

### 9.6.1.3 Grading of Adenocarcinoma

No histologic grading system with specific criteria is established for lung adenocarcinoma. However, prognostic grading is applied with the single most predominant pattern as follows; low-grade (lepidic), intermediate grade (acinar and papillary) and high-grade (solid and micropapillary) [29, 60].

### 9.6.1.4 Introducing the Spread Through Air Spaces

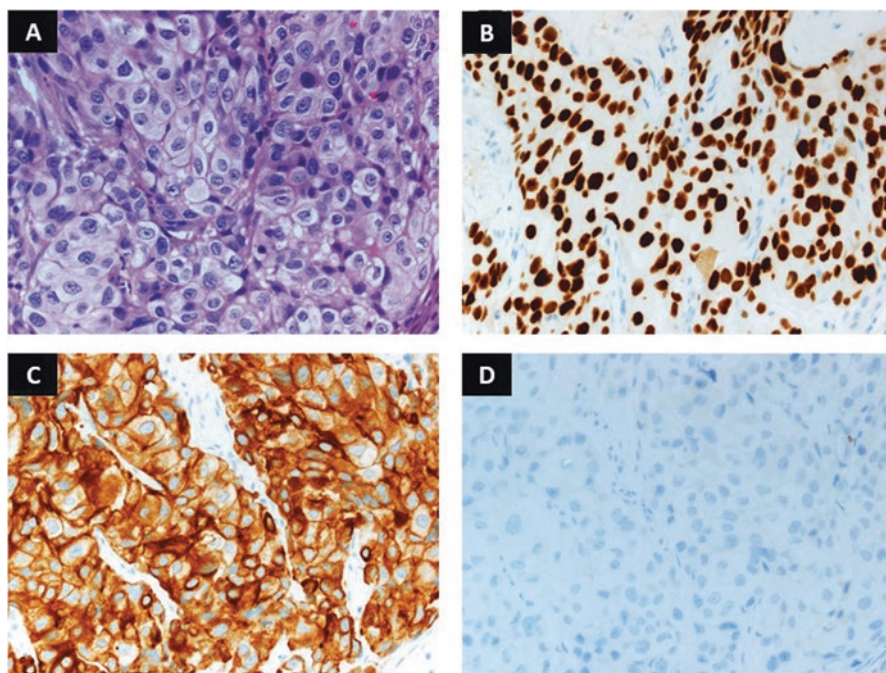
Spread through air spaces (STAS) is an additional pattern of invasion to be reported. It is characterized by micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma. It is not included in the percentage measurement of subtyping or in measurement of invasive size [29].

## 9.6.2 Squamous Cell Carcinoma (SQCC)

SQCC is a malignant tumor originated from bronchial epithelial cells with keratinization and/or intercellular bridges. SQCC has 3 subtypes; keratinizing, nonkeratinizing and basaloid [62]. If a tumor presents with any amount of keratinization, it is keratinizing subtype. While the basaloid SQCC is diagnosed when this component is greater than 50% of the tumor, regardless of the presence of keratinization. Nevertheless, there is no significant difference of prognosis among each subtype [29].

### 9.6.2.1 Gross Pathology

Most SQCCs are centrally located with white to gray discoloration depending on the extent of fibrosis. Large peripheral SQCCs often display necrosis and cavitation. Central tumors usually show intraluminal polypoid growth and may occlude the bronchial lumen. Bronchiectasis, atelectasis, and infective bronchopneumonia are frequently observed in the lung distal to the obstruction (Fig. 9.3).



**Fig. 9.3** Role of immunohistochemistry in lung carcinoma. (a) H&E staining shows solid sheets of large polygonal tumor cells with clear or eosinophilic cytoplasm and distinct cellular border. Neither glandular formation nor squamous differentiation is identified. (b) The immunostaining for TTF-1 reveals positive result and confirms the diagnosis of solid adenocarcinoma. The tumor cells display strong expression for CK7 (c) but no expression for CDX-2 (d). These results support primary lung adenocarcinoma in this case and also exclude the possibility of metastatic colonic adenocarcinoma to lung

**Table 9.9** Summary of immunohistochemical stains in the differential diagnosis of poorly differentiated carcinoma of lung

	TTF-1	Napsin A	p63	P40
Adenocarcinoma	+ <sup>a</sup>	+ <sup>a</sup>	–	–
Squamous cell carcinoma	–	–	+	+

*TTF-1* thyroid transcription factor 1

<sup>a</sup>Negative in rare cases

### 9.6.2.2 Histopathology

SQCC is characterized by cytoplasmic keratinization, pearl formation, and intercellular bridges. These features vary with degree of differentiation, being prominent in previously called well-differentiated squamous cell tumors and focal in poorly differentiated tumors [61]. An immunohistochemistry staining is helpful to distinguish poorly differentiated SQCC from adenocarcinoma using thyroid transcription factor 1 (TTF-1), Napsin A, p40 and p63 (Table 9.9).

### 9.6.2.3 Grading of SQCC

There is a limited number of studies but nuclear diameter is revealed to be an independent factor of worse outcome [63].

## 9.6.3 Large Cell Carcinoma (LEC)

LEC is an undifferentiated carcinoma without cytologic and architectural features of typical small cell carcinoma (SCC) and glandular or squamous differentiation. This entity is very rare and rather a diagnosis of exclusion. A poorly differentiated carcinoma without histomorphologic evidence of glandular differentiation or intracytoplasmic mucin that reveals “adenocarcinoma markers” expression by IHC (such as TTF-1 and/or Napsin A) has to be diagnosed as a solid adenocarcinoma. On the other hand, a poorly differentiated carcinoma that has no histomorphologic evidence of squamous differentiation but is immunoreactive to “SQCC markers” such as p40, p63 or CK5/6, has to be diagnosed as non-keratinizing SQCC [36].

### 9.6.3.1 Gross Pathology

LECs usually present as large, peripheral mass, often invade visceral pleura, chest wall, or adjacent structures. Typical cut surface is gray-tan tumor with frequent necrosis and occasional hemorrhage.

**Table 9.10** Immunohistochemical stains for differential diagnosis of metastatic lesion or unknown origin

	CK7	CK20	TTF-1	CDX2	GCDFP-15	CEA	Mucin
Lung	+	–	±	–	–	–	MUC5AC-
Breast	+	–	–	–	+ or ER+	–	–
Colorectum	-	+	-	+			
	-	-	-	+		+	MUC2+
Stomach	+	–	–	+			
Ovary	+		–	–	–	–	MUC5AC+
Pancreaticobiliary tract	+	–	–	–		+	MUC5AC+

Note: *CK* cytokeratin, *TTF-1* thyroid transcription factor 1, *GCDFP* gross cystic disease fluid protein, *CEA* carcinoembryonic antigen, *ER* estrogen receptor.

Modified from Park SY et al. [157].

### 9.6.3.2 Histopathology

Characteristic features are sheets or nests of large polygonal cells with vesicular nuclei, prominent nucleoli, and a moderate amount of cytoplasm.

## 9.6.4 Metastatic Tumors to the Lung

Secondary tumors in the lung are more common than primary lung neoplasms. Detecting the organ of origin is frequently difficult, particularly metastatic adenocarcinoma of unknown primary. Multiple-marker panels of immunohistochemical stains are developed to predict the primary site as shown in Table 9.10.

## 9.7 Treatment Approaches

A multidisciplinary approach for NSCLC is recommended for achieving intense curative treatment including surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy. Choosing a treatment modality mainly depends on the stage of disease and patient status.

### 9.7.1 Surgery

#### 9.7.1.1 Surgery for Early Stage NSCLC (Stage I and Stage II)

Surgery is a primary approach for early stage NSCLC if there are no contraindications. Anatomical resection such as lobectomy is recommended. Sleeve or bronchoplastic resection is recommended more than a pneumonectomy because it effects on



the quality of life(QOL) and no greater survival benefit. The recent ACCP and NCCN guideline recommended that surgery should be performed by a board certified thoracic surgeon with a focus on lung cancer (at least 75% of practice is general thoracic surgical procedures and an average performance of at least 4 anatomical resections per month) [64]. Systematic mediastinal LN sampling (SLNS) or dissection (SLND) should be done simultaneously with anatomical resection. There are no statistically significant differences between these 2 methods in terms of DFS after complete resection in Stage I NSCLC patients as proven by the largest RCT study [65]. For clinical Stage II, SLND may provide an additional survival benefit rather than SLNS [64]. In the SLNS, IASLC recommended 3 MLN stations (N2 nodes), one of which must be the subcarinal node (station7), and 3 of N1 nodes/stations should be sampled [64]. In the SLND, at least 3–5 of N2 stations, one of which must be station 7 and at least 10–16 LNs including both N1 and N2 nodes have been recommended [66, 67]. Currently, lobe-specific nodes dissection (L-SND) have been proposed (except RML because of no specific lymphatic pattern) based on the location of primary tumor (stations 7,8 and 9 for both lower lobe, station 2R,3 and 4R for RUL, station 4 L, 5 and 6 for LUL). However, there are some evidences from retrospective studies reported about occult N2 disease and skip metastasis, a well-designed prospective RCT comparing L-SND to SLND in patients with clinical stage I-II NSCLC is currently ongoing in Japan (JCOG1413) [68].

There are 3 surgical approaches for lung cancer surgery; conventional open thoracotomy, VATS and robotic surgery. A surgeon can perform all approaches utilizing oncologic principles. Many studies confirmed that the VATS and robotic approaches are safe, can achieve oncologic principles. The advantages of these approaches are a shorter hospital stay and reaching a 5-year OS and DSF compared to an open thoracotomy [69, 70]. Single-port VATS are now feasible in well selected patients with similar operative time, blood loss, duration of chest tube drainage, and length of hospital stay to multi-port VATS [71]. However, RCTs are needed.

Sublobar resection (segmentectomy if possible) with 2 cm gross margins can be performed in clinical stage I NSCLC who had poor pulmonary reserve, defined as having maximal oxygen consumption ( $VO_2$  max) < 10 mL/kg/min, or the combination of  $VO_2$  max <15 mL/kg/min with both FEV1 and DLCO <40% predicted post-operative (PPO) function [64, 72]. For patients whom adequate margin could not be achieved, the addition of brachytherapy mesh to a sublobar resection may improve local control. Recent study [73] found that segmentectomy and lobectomy had equivalent survival for patients with clinical Stage IA.

### 9.7.1.2 Surgery for Locally Advanced Stage (Stage III)

The role of surgery in Stage III NSCLC is still debatable because of heterogeneity of N2 disease. Currently, surgery can be performed in patients with  $T_{3-4}N_{0-1}M_0$  or  $T_{1-3}N_2M_0$ , resectable with R0 resection, single station microscopic N2, selected multi-station N2 if microscopic N2 and nodal disease is radical surgical resection. In these cases, induction chemotherapy or chemoradiotherapy should be first

considered and followed with R0 resection. The advantage of induction therapy is to downstage the tumor. Restaging of lung and mediastinum after induction therapy is necessary to assess response, confirm resectability and exclude disease progression. The diagnostic procedures and their diagnostic index were shown in Table 9.11. There are some evidences that pN0 disease after induction therapy had a better OS than pN1–3 disease [74]. The results from recent meta-analysis stated that radiotherapy plus chemotherapy were not superior to neoadjuvant chemotherapy alone [75]. Moreover, radiation may be undesirable if sleeve resection of bronchus or artery, or pneumonectomy, especially for right-sided is planned [76]. The contraindications to surgery included a large (> 3–5 cm) “bulky” N2, multiple matted N2 that cannot be individually discerned, continuous with the primary tumor and encase mediastinal vessels or airways, or unfitted patients [77]. Preoperative induction therapy did not significantly affect morbidity or mortality [78]. The recommended approach is open thoracotomy, however; VATS can be safely performed in selected cases with lower estimate blood loss, shorter duration of chest drainage, shorter LOS [79] and similar OS or DFS to open thoracotomy approach [80]. In case of persistent disease after surgery, postoperative RT with chemotherapy should be performed [81]. If patients with resectable N2 disease(IIIA) identified preoperatively, induction therapy followed by surgery is recommended, however, if incidental (occult) N2 disease was found at surgical resection despite fully preoperative staging methods, planning for complete resection with SLND should be continued because of achieving 87% of 3-year survival and 81% of 5-year survival [82, 83]. Surgical resection in stage III NSCLC should be performed under a discussion of the multidisciplinary team. Pneumonectomy should be avoid as much as possible because of high mortality and morbidity, therefore in case of planning for pneumonectomy after induction therapy, patients should be advised of increased operative risk, the postoperative mortality was 21% and a predictor of postoperative mortality was a postoperative bronchopleural fistula [84].

**Table 9.11** Diagnostic procedures and their diagnostic index for restaging of the mediastinum in patients with lung cancer after neoadjuvant therapy

Procedures	False negative (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CT	50–65	38–94	31	–	–	–
Pet	36	50–76	85–90	–	–	–
EBUS-TBNA	12.5–58	44–84	60–100	33–100	42–88	60–89
TEMLA	–	96.6	100	100	98.5	–
Repeated mediastinoscopy	22	29–71	100	–	–	60–88
Primary mediastinoscopy	9	89	–	–	–	–
VATS	24–33	62	100	–	–	–

Data from Cetinkaya E et al., Nasir BS et al., Genestreti G et al., von Bartheld MB et al., De Waela M et al., and Detterbeck FC et al. [158–163]

### 9.7.1.3 Surgery for Stage IV

The treatment for Stage IV NSCLC is multimodality treatment, including chemotherapy, radiotherapy, targeted therapy and immunotherapy. Surgery may be a role in some circumstances especially patients suffered from its complication such as massive hemoptysis or obstructive pneumonitis, however, risk and benefit should be considered especially in case of T4 which tumor invade vital structures such as the heart, main trunk of pulmonary artery or main bronchus. The role of surgery in stage IV NSCLC is focused on a synchronous brain metastasis. Recent study demonstrated that 5-year overall survival was up to 21% in patients with controlled primary tumor after resection of brain metastasis or receiving SBRT [85]. An OS rates of bifocal surgical resection were 79, 42, and 8% at the 1st, 2nd, and 5th years, respectively. The most benefit from surgery will occur when no MLN involvement or any other extrathoracic spread [86]. Gamma-knife radiosurgery (GKS) can be used effectively and beneficially instead of conventional brain surgery. General indication for using GKS for brain metastasis in lung cancer include; (1) Karnofsky Performance Scale (KPS)  $\geq 70$ ; (2) estimated life expectancy  $\geq 4$  months; (3) no rapidly evolving intracranial mass effect; (4) three or fewer lesions with maximum diameter  $\leq 3$  cm; (5) target(s) well defined on the neuroimages; (6) stage I or II of NSCLC; and (7) no extracranial metastasis [87, 88]. Recent study demonstrated that GKS combined with crizotinib showed effective local tumor control and excellent outcome, especially in oligometastases [89].

### 9.7.2 Radiosurgery

Stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) has been increasingly recognized as a favorable alternative to surgical resection for inoperable early-stage NSCLC [90]. The recent meta-analysis demonstrated that stage I-II NSCLC patients with SBRT achieved superior OS, DFS, local, regional, locoregional, and distant control survival, compared with surgery [90]. The American Society for Radiation Oncology (ASTRO) developed the guideline recommendation for appropriate use of SBRT stated that for patients with standard operative risk (operative mortality  $<1.5\%$ ), SBRT is not recommended as an alternative to surgery outside of a clinical trial. For stage I patients with high operative risk, discussions about SBRT as a potential alternative to surgery are encouraged. For centrally located tumor, SBRT should be delivered in 4 or 5 fractions or 6–15 fractions in very high risk. For patients with tumors  $>5$  cm in diameter with an acceptable therapeutic ratio, SBRT is an appropriate option. Tissue diagnosis procedure is recommended, but in patients who refuse a biopsy or who are thought to be at prohibitive risk of biopsy, discussion in a multidisciplinary manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lung lesion based on tumor, patient, and environmental factors are recommended. SBRT is recommended as a curative treatment option for patients with

metachronous multiple primary lung cancer with equivalent rates of local control and toxicity and overall survival compared with those with single tumors [91].

### **9.7.3 Chemotherapy, Radiotherapy, Targeted Therapy and Immunotherapy**

#### **9.7.3.1 Early Stage**

##### 9.7.3.1.1 Adjuvant Therapy

Locoregional recurrence after completely resection of tumor is common in approximately 20–25% in Stage I–II and up to 50% in Stage III, adjuvant platinum-based chemotherapy has become standard in patients with Stage II and IIIA NSCLC. Cisplatin combination with vinorelbine had the greater effect on OS when compared with other drugs [92]. If surgical margin is positive or inadequate mediastinal LN dissection, postoperative radiation is considered [93].

#### **9.7.3.2 Locally Advanced Stage**

##### 9.7.3.2.1 Sequential or Concurrent Chemotherapy and Radiation

In patients with unresectable locally advanced or medically inoperable Stage III NSCLC and good performance status, a CCRT with platinum-based is preferred to sequential chemotherapy and radiation (SCRT). Median survival (MS) was 14.6 months for SCRT versus 17 months in CCRT [94]. For definitive radiation, standard dose RT (60 Gy) is commonly used and OS is similar to high dose radiation (74 Gy) [95].

##### 9.7.3.2.2 Consolidation after CCRT

Durvalumab, an anti-programmed death ligand 1 (PD-L1) antibody showed better DFS, Response rate (RR), median time to death, and median time to distant metastases than placebo as a consolidation therapy in patients with unresectable stage III NSCLC, physical status 0–1 who did not have disease progression after 2 or more cycles of definitive chemoradiotherapy, an OS is awaited, however the accepted toxicity profile of immunotherapy and double PFS over placebo from the RCT make it should be the new standard in this clinical setting. NCCN guideline version 1.2018 already included Durvalumab as a consolidation therapy for these patients (10 mg/kg IV every 2 weeks for up to 12 months) [96].

### 9.7.3.2.3 Neoadjuvant Chemotherapy Followed by Surgery

The results from recent meta-analysis showed that a neoadjuvant chemotherapy arm provided better OS, DFS, and improved R0 resection rates than upfront surgery arm in resectable NSCLC (stage I-IIIa, excluded T1 N0) [97]. The delivery of chemotherapy is more difficult in the adjuvant therapy when compared with preoperative chemotherapy as demonstrated in NATCH phase III trial [98].

### 9.7.3.2.4 Radiotherapy

Radiotherapy alone is considered in patients who are not fit for chemotherapy or with poor performance status.

## 9.7.3.3 Advanced Stage

### 9.7.3.3.1 Chemotherapy

Meta-analyses have proved that platinum-based chemotherapy improves OS when compared with best supportive care (BSC) and gain MS time from 4.5–6 months and increased 1 year survival from 20% to 29% [99]. Doublet combination of second generation chemotherapy with platinum-based regimen for 4–6 cycles is the standard of care in advanced NSCLC. The second generation drugs such as docetaxel, gemcitabine, paclitaxel and vinorelbine are used in combination with platinum [100]. The RCT showed similar outcomes in term of RR, PFS and OS of second generation chemotherapy either paclitaxel or gemcitabine or docetaxel in combination with platinum [101]. Phase II trial demonstrated that non-platinum based chemotherapy had inferior PFS to platinum-based regimen. However, phase 3 trial data show no statistically difference in MS between platinum or nonplatinum doublet chemotherapy [100]. From recent phase III studies showed carboplatin had similar OS when compared to cisplatin and appears less toxic, especially nausea, vomiting and nephrotoxicity [102, 103]. In patients with non-squamous NSCLC (adenocarcinoma and large cell) pemetrexed/cisplatin had a statistically significant better survival than gemcitabine/cisplatin [104], but similar to docetaxel/cisplatin [105]. However, patients with SQCC the pemetrexed/cisplatin regimen had inferior survival to gemcitabine/cisplatin. In patients with performance status at least two are usually treated with single agent chemotherapy includes gemcitabine, pemetrexed, taxanes or vinorelbine. Combination chemotherapy regimens include paclitaxel/carboplatin, pemetrexed/carboplatin from RCT had significantly improve OS when compare with single agent pemetrexed alone with median OS was P = 5.3 mo vs. CP = 9.3 mo (HR = 0.62, 95% CI 0.46; 0.83, p = 0.001) [106]. However, some patients had treatment-related deaths.

### 9.7.3.3.2 Molecular Therapy (Targeted Therapy)

#### *First Line Setting*

#### EGFR –Targeted Agents

In NCCN guideline v.12018, targeted agents and immunotherapy in first line and subsequent lines in NSCLC was shown in Table 9.10. A large RCT compared EGFR-TKI (gefitinib) with standard chemotherapy (paclitaxel/carboplatin) in first line setting of light or never smoked, Stage IIIB or IV adenocarcinoma of lung. PFS was significantly better with gefitinib in EGFR mutation group, however OS is not difference between gefitinib and standard chemotherapy. The most common adverse events in the gefitinib group were rash or acne (66.2%) and diarrhea (46.6%), whereas neutropenia, neurotoxicity (69.9%), neutropeia (67.1%) and alopecia (58.4%) were frequently found in paclitaxel/carboplatin arm [107]. Interstitial pneumonitis is the uncommon serious adverse event of EGFR-TKI that should be monitored in addition to progression of disease or other causes. The randomized Phase 3 study evaluated EGFR-TKI (erlotinib) versus standard chemotherapy in adenocarcinoma of lung stage IIIB/IV harbouring activating EGFR mutation. The result showed a significant improve PFS in patients received erlotinib and better tolerability when compared to chemotherapy arm [108]. There were no significant difference in term of efficacy and toxicities between erlotinib and gefitinib [109].

Afatinib is an irreversible ErbB family blocker and was studied compared to chemotherapy (pemetrexed/cisplatin) in patients with adenocarcinoma of lung whose tumors harboured EGFR mutation. The results from the LUX-Lung3 trial showed that afatinib group had prolongation of PFS with median PFS of 11.1 months versus 6.9 months in the chemotherapy arm (HR, 0.47; 95% CI, 0.34–0.65). The most common adverse events of afatinib were diarrhea, rash/acne, and stomatitis/mucositis [110].

Osimertinib is a third generation EGFR-TKI selective for inhibit EGFR sensitizing and T790 M resistance mutation. A FLAURA trial comparing osimertinib with gefitinib or erlotinib as first line therapy in locally advanced or metastatic EGFR axon 19 or 21 mutation NSCLC patients. The results showed statistically better PFS for osimertinib arm. Regarding safety, tolerability and CNS efficacy make it possible to be a new standard EGFR-TKI, however result of OS and resistance mechanism are awaited [111]. Osimertinib is also recommended for second line and beyond after first or second generation EGFR-TKI who had T790 M mutation [112].

#### *ALK Rearrangement-Targeted Agent*

Crizotinib, an ALK inhibitor, has been shown to be effective against ALK positive.

NSCLC. From Phase II study (PROFILE 2005) in second and third line treatment showed dramatic responses of 60% with a median PFS of 8.1 months. The common adverse events were edema, dizziness, nausea, decreased appetite, diarrhea, constipation, visual effects, increased liver transaminases and fatigue. It is also c-MET inhibitor and ROS1 inhibitor [113]. Crizotinib, had efficacy in second or

third line setting NSCLC after previous chemotherapy. The overall RR and stable disease are 57% and 33% respectively. The 1 and 5 year overall survivals are 74% and 54% respectively [114].

Ceritinib [115], alectinib [116] and brigatinib [117] which are second generation of ALK inhibitor played role in patients who had progressed on crizotinib. From ASCEND- 4 trial, ceritinib was approved for first line therapy from higher overall (73% vs 27%) and intracranial RR (57% vs 22%), better PFS (16.6 vs 8.1 mo) than chemotherapy [118]. Alectinib has been approved for first line agents for ALK-positive metastatic NSCLC. Based on ALEX trial [119], ceritinib had better PFS than crizotinib (25.7 vs 10.4 mo), CNS RR (81 vs 50%) and marked reduction risk of brain metastasis. From phase II ALTA trial, brigatinib 180 mg/day had better clinical benefit than 90 mg/day with RR 54%, intracranial response 67%, PFS 12.9 months and 1 year OS 80% [120].

Lorlatinib, third generation ALK inhibitor showed remarkable benefit after failure crizotinib and ceritinib. Lorlatinib could resensitized patients to crizotinib after lorlatinib failure [121].

#### *Anti-EGFR Antibody*

A monoclonal antibody (Cetuximab) targeting the EGFR was assessed in advanced NSCLC patients in FLEX and BMS099 trial. The data demonstrated that the addition of cetuximab to standard chemotherapy (cisplatin/vinorelbine in FLEX and taxane/carboplatin in BMS099) prolonged OS for a median of 9.7–11.0 months compared with 8.4–10.0 months for chemotherapy alone. However, the benefit was slightly improved survival and it was not clinically significant [122, 123].

Necitumumab, a second generation IgG1 EGFR Ab, in combination with gemcitabine/cisplatin showed improve OS than chemotherapy alone (11.5 vs 9.9 mo). It was approved for first line treatment of metastatic squamous lung cancer. Skin rash and hypomagnesemia are adverse events more common found in necitumumab arm [124].

#### *Antiangiogenesis Agents*

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). Bevacizumab combined with paclitaxel-based regimen is another choice for patients with non-squamous advanced NSCLC based on the results from phase II trial (ECOG 4599) with statistically improved OS. The MS was 12.3 months in bevacizumab combination with chemotherapy group versus 10.3 months in chemotherapy without bevacizumab group. The meta-analysis showed that bevacizumab prolongs the PFS and OS when added to doublet platinum-based chemotherapy [125]. OS benefit was found only in combination of bevacizumab and paclitaxel/carboplatin and should not be used in SQCC and recent history of hemoptysis. Other anti-angiogenic agents such as Vandetanib, a small molecule inhibitor of VEGF signaling, EGFR and RET or sorafenib showed no benefit in OS [126].

### *Maintenance Therapy*

Maintenance therapy has two approaches, switch maintenance and continuous maintenance therapy. The first is the transition from standard platinum-based chemotherapy to different chemotherapy or targeted therapy. The second is to continue non-platinum chemotherapy of the initial platinum-based regimen. From RCTs, switch maintenance therapy with pemetrexed [127] or erlotinib [128] or continuation maintenance with bevacizumab [129], cetuximab [122], pemetrexed [130], had significantly improvement in PFS and OS when given in patients who did not progress after four cycles of platinum-based chemotherapy. For erlotinib maintenance [128], the overall benefit was significantly better in patients with EGFR mutations and stable disease after first line chemotherapy, but not in responder patients. Other drugs such as switch maintenance with docetaxel [131] or continuation maintenance with gemcitabine [132] or bevacizumab/pemetrexed [133] had been tested and found that they improve PFS but not for OS. Maintenance treatment is not a standard of care, just only an option in some patients.

### *Second Line and Third Line Systemic Treatment*

Platinum based chemotherapy with or without bevacizumab is a choice for second line therapy after failure from first line targeted agents (EGFR-TKI or ALK inhibitor). Second or third line treatment, both docetaxel and pemetrexed (only for non-squamous cell carcinoma) are recommended in patients who had progression of disease, if chemotherapy had never been given and with performance status of zero to two. Randomized studies demonstrated the OS and QOL improvement with docetaxel compares with ifosfamide, vinorelbine or BSC [134, 135]. Pemetrexed showed less toxicity, similar in RR, PFS, and OS [136]. A meta-analysis study compared single agent with combination chemotherapy in second line treatment. Results showed that combination chemotherapy had significantly improved RRs and PFS, but not improve OS and increased toxicity [137].

The combination of nintedanib (a triple angiokinase inhibitor) or ramucirumab (VEGFR antagonist) with docetaxel significantly improved OS in second line advanced NSCLC therapy and in refractory to prior first-line treatment [138]. Nintedanib/docetaxel had longer PFS (4 vs 2.8 mo) and OS than standard arm (13.5 vs 10.3 mo) in adenocarcinoma histology. Grade 3 or worse diarrhea and reversible increase in liver enzyme were more frequent in nintedanib group [139]. Ramucirumab/docetaxel improved survival 1.4 months when compared with docetaxel alone [140].

Regarding targeted agents, BR.21 trial tested between erlotinib (EGFR-TKI) versus BSC in second or third line treatment, the OS was better in the erlotinib arm with median OS 6.7 months versus 4.7 months in BSC arm [141]. Gefitinib (EGFR-TKI) demonstrated non-inferior OS when compares with docetaxel [142].



### 9.7.3.3.3 Immunotherapy

An immunotherapy has the potential to improve immune-PFS and OS based on nonrandomized and randomized Phase II and Phase III trials. Current standard of anti-PD1 and anti PD-L1 immunotherapy in advanced NSCLC are shown in Table 9.11. The anti-EGF vaccine evaluated in randomized Phase IIB study with stage IIIB/IV NSCLC patients who completed first-line chemotherapy trended toward improved survival when compared with the control group [143]. The Mycobacterium vaccine (SRL172) administered concurrently with chemotherapy for six cycles followed by maintenance or control group in randomized Phase III with advanced NSCLC had a significantly improved QOL and OS only in adenocarcinoma patients [144]. GVAX vaccine evaluated in nonrandomized early and advanced NSCLC found that 9.1% of patients achieved complete response and prolonged remission and 80% of early stage had DFS > 12 months [145]. Lucanix evaluated as a phase II nonrandomized trial in early and advanced NSCLC found 15% response and increased survival [146]. Stimuvax evaluated in randomized phase II trial showed no statistical difference in OS but trended to improve MS in stage IIIB locoregional disease [147]. MAGE-A3 Antigen-Specific Cancer Immunotherapy was studied in randomized Phase IIB trial and showed non-statistical significance delayed time to recurrence (35.0% in vaccine group versus 43.0% in control group) [148]. This interesting result introduced MAGE-A3 for the investigation of the efficacy in preventing cancer relapse in large randomized Phase III trial (MAGRIT). TG410 vaccine is a recombinant virus expressing MUC1 antigen and IL-2. It was tested in Phase II study and showed enhancement of the effect of chemotherapy by a improved RR and trended to improve PFS [149]. Ipilimumab is a fully human monoclonal antibody that stimulates immunity by anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4). From phase II study, Ipilimumab when used concurrent or phased ipilimumab combined with chemotherapy showed improved median immune-related PFS. It was 5.68 months for the phased ipilimumab group versus 4.63 month for chemotherapy alone group (HR 0.68,  $p = 0.02$ ) and 5.52 months for concurrent ipilimumab group versus 4.63 for chemotherapy alone group (HR = 0.77,  $p = 0.09$ ). The important adverse events were hypophysitis, enterocolitis and hyperthyroidism which may be improved with steroids. However, in phase III trials, the addition of ipilimumab to first-line chemotherapy did not prolong OS compared with chemotherapy alone in patients with advanced SQCC [150]. The combination of nivolumab plus ipilimumab as first line therapy has shown a tolerable safety profile and encouraging clinical activity characterized by a high RR and durable response compared with anti-PD-1 monotherapy from the open-label, phase 1, multicohort study(CheckMate 012) cohorts [151]. Waiting for a phase 3 trial supporting of this combination is needed (Table 9.12).

**Table 9.12** Targeted agents and immunotherapy in first line and subsequent lines in NSCLC

Targeted group	First line therapy	Subsequent therapy
Sensitizing EGFR mutation	Afatinib, Erlotinib, Gefitinib, Osimertinib	Osimertinib
ALK rearrangement	Alectinib, Ceritinib, Crizotinib	Alectinib, Brigatinib, Ceritinib
ROS1 rearrangement	Ceritinib, Crizotinib	
BRAF V600E mutation	Dabrafenib/trametinib	Dabrafenib/trametinib

Adapted from NCCN guideline v 1.2018

#### 9.7.3.3.4 Radiation for Palliative Treatment

Palliative radiotherapy is an important option for patients with symptomatic metastatic stage or locally advanced stage not suitable for curative treatment. Radiotherapy has demonstrated the benefit to improve respiratory problems such as hemoptysis, dyspnea, tracheal or bronchial compression and chest pain. Palliative radiotherapy also plays role in painful bone metastases, symptomatic brain metastases and superior vena cava syndrome [100, 152]. High dose rate brachytherapy provided better symptomatic palliative treatment especially in patients with endobronchial lesion rather than external beam radiation alone [153] (Table 9.13).

## 9.8 Conclusion

The incidence of lung cancer continues to increase but its mortality has plateaued or slightly decreased which may be due to improvement in multidisciplinary treatment. Low-dose CT screening in high risk patients is a very interesting issue for early detection of lung cancer and has reduced the overall mortality. Further studies should be continued for the evaluation of cost-effectiveness. Staging workup techniques are very important for definite diagnosis and planning of treatment. Multimodality treatment including surgery, radiosurgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy should be considered in all stages of NSCLC. The aims of treatment are for cure, especially in early stages, or at least to prolong survival and improve the QOL in advanced disease.

### Key Points

- Lung cancer screening with low-dose CT scan have a benefit for early detection of lung cancer in high-risk patients and was recommended in many guidelines such as NCCN, AATS, ASCO, ESMO, ACS, USPSTF, ACCP guidelines etc.
- The integrated PET/CT scan should be performed in all lung cancer cases, not only differentiate between malignant and benign tumor, but also is the most excellent noninvasive technique for nodal and distant metastatic detection.
- Needle techniques such as EBUS, EUS, TBNA have an important role for mediastinal staging work up and should be performed before surgical technique.

**Table 9.13** FDA approval immunotherapy in advanced NSCLC

Agent	Target	Trial	Setting	OS	PFS	RR (%)	Treatment-related AE
<b>First line</b>							
Pembrolizumab vs chemotherapy	PD1	KN-024 RCT phase III <sup>a</sup>	Non-squamous & squamous PD-L1 ≥ 50% 1 <sup>st</sup> endpoint: PFS	6 mo; 80.2% vs 2.4% HR 0.6 (95%CI 0.41–0.89)	Median PFS 10.3 vs 6mo HR 0.5 (95% CI 0.37–0.68)	44.8 vs 27.8	73.4% vs 90%
Pembrolizumab/ carboplatin/Pemetrexed vs Carboplatin/Pemetrexed	PD1	KN-021 RCT phase II <sup>b,c</sup>	Non-squamous, any PDL1 1 <sup>st</sup> endpoint: RR	Median OS NR vs 20.9 HR 0.59 (95%CI 0.34–1.05) 18 mo OS; 70% vs 56%	Median PFS 19 vs 8.9 mo	56.7 vs 31.7	G3–5 Tx related 41% vs 29%
<b>Subsequent line</b>							
Nivolumab vs Docetaxel	PD1	CM017 RCT Phase III <sup>d,e</sup>	Squamous, any PDL1 1 <sup>st</sup> endpoint: OS	Median OS 9.2 vs 6 mo HR 0.59 (95%CI 0.44–0.79)	Median PFS 19 vs 8.9 mo	20 vs 9	Any grade 58% vs 86% G3–4 7% vs 55%
Nivolumab vs Docetaxel	PD1	CM057 RCT phase III <sup>e,f</sup>	Non-squamous, any PDL1 1 <sup>st</sup> endpoint: OS	1 year OS 42% vs 24% 2 year OS 23% vs 8% Median OS 12.2 vs 9.4 mo HR 0.73 (95%CI 0.59–0.89) 1 year OS 51% vs 39% 2 year OS 29% vs 16%	Median PFS 2.3 vs 4.2 mo 1 year PFS 19% vs 8% 2 year PFS 12% vs 1%	19 vs 12 p = 0.02	2 year AE G3–4 10% vs 54%

(continued)

**Table 9.13** (continued)

Agent	Target	Trial	Setting	OS	PFS	RR (%)	Treatment-related AE
Pembrolizumab 2 mg/kg vs 10 mg/kg vs docetaxel	PD1	KN-010 RCTphaseII/ III <sup>g,h</sup>	Advanced NSCLC, PDL1: TPS ≥ 1%, 1 <sup>vy</sup> endpoint: OS, PFS	Median OS Overall 10.4 vs 12.7 vs 8.5 mo HR 0.71 (95%CI 0.58–0.88) (2 mg vs Docetaxel) HR 0.61 (95%CI 0.49–0.75) (10 mg vs Docetaxel) <b>TPS ≥ 1%</b> 10.5 vs 13.6 vs 8.6 mo <b>TPS ≥ 50%</b> 14.9 vs 17.3 vs 8.2 mo HR 0.54 (95%CI 0.38–0.77) (2 mg vs Docetaxel) HR 0.50 (95%CI 0.36–0.70) (10 mg vs Docetaxel) <i>At 18 mo OS</i> <b>TPS ≥ 1%</b> 37% vs 43% vs 24% mo <b>TPS ≥ 50%</b> 46% vs 52% vs 24%	Median PFS Overall 3.9 vs 4.0 vs 4.0 mo HR 0.88 (95%CI 0.74–1.05) (2 mg vs Docetaxel) HR 0.54 (95% 0.38–0.77) (10 mg vs Docetaxel) <b>TPS ≥ 50%</b> 5.0 vs 5.2 vs 4.1 mo HR 0.59, 95% CI 0.44–0.78 (2 mg vs Docetaxel) HR 0.59 (95%CI 0.45–0.78) (10 mg vs Docetaxel)	<b>TPS ≥ 1%</b> 19 vs 20 vs 10 <b>TPS ≥ 50%</b> 29 vs 32 vs 9	AE G3–5 13% vs 16% vs 35%

Atezolizumab vs docetaxel	PD-L1	POPLAR RCT phase II <sup>a</sup> OAK trial RCT phase III <sup>b</sup>	Advanced NSCLC, any PDL1 Advanced NSCLC, any PDL1	Median OS 12.6 vs 9.7 mo HR 0.73 (95% CI 0.53–0.99) Median OS 13.8 vs 9.6 mo HR 0.73 (95% CI 0.62–0.87) <i>Non-squamous</i> 15.6 vs 11.2 mo <i>Squamous</i> 8.9 vs 7.7mo	G3–4AE 11% vs 39% G3–4AE 15% vs 43%
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PFS = progression-free survival, OS = overall survival, RR = response rate, HR = hazard ratio, NR = not reach, Tx = toxicity, TPS = tumor proportion score

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<sup>b</sup>Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497–508

<sup>c</sup>H. Borghaei CJL, S. Gadgeel, V.A. Papadimitrakopoulou, A. Patnaik, S.F. Powell, R.D. Gentzler, R.G. Martins, J.P. Stevenson, S.I. Jalal, A. Panwalkar, J.C. Yang, M. Gubens, L. Sequist, M.M. Awad, J. Fiore, S. Saraf, H. Raftopoulos, L. Gandhi. Updated results from KEYNOTE-021 cohort G: a randomized, phase 2 study of pemetrexed and carboplatin (PC) with or without pembrolizumab *Annals of Oncology.* 2017;28(Supplement 5):v605-v49

<sup>d</sup>Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-small-Cell Lung Cancer. *N Engl J Med.* 2015;373(2):123–35

<sup>e</sup>Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J Clin Oncol.* 2017;35(35):3924–33

<sup>f</sup>Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-small-Cell Lung Cancer. *N Engl J Med.* 2015;373(17):1627–39

<sup>g</sup>M-J.A. Ahn M, Majem M.J. Fidler G, De Castro M, Garrido Y, Shentu G.M. Lubiniecki E.B. Garon RSHPB-D-WKEFILP-GJ-YHJM-J-HKCD.A. Pembrolizumab (pembro) vs docetaxel (doce) for previously treated, PD-L1-expressing NSCLC: Updated outcomes of KEYNOTE-010. *Annals of Oncology.* 2016; 27(Supplement 6)

<sup>h</sup>Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387(10027):1540–50

<sup>i</sup>Fehrenbacher L, Spira A, Ballinger M, Kowanzet M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet.* 2016;387(10030):1837–46

<sup>j</sup>Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 2017;389(10066):255–65

- Lobectomy with systematic LN dissection or sampling is a standard of surgical treatment for early stage NSCLC; however, sublobar resection or SBRT can be done in selected poor pulmonary-preserved patients.
- Surgery can be performed after induction therapy in patients with  $T_{3-4}N_{0-1}M_0$  or  $T_{1-3}N_2M_0$ , resectable with R0 resection, single station microscopic N2, selected multi-station N2 if microscopic N2 and nodal disease is radical surgical resection.
- New targeted and immunotherapy have been proposed and some drug have already proved as the first, second or third line of treatment in selected advanced NSCLC patients.

### Multiple-Choice Questions

1. What is the imaging of choice to evaluate the patients with NSCLC?
  - (A) PA upright and lateral chest radiographs
  - (B) Chest CT scan
  - (C) Low dose chest CT scan
  - (D) Chest MRI
  - (E) Integrated PET/CT

Answer: (B)

Chest-CT scan is the imaging modality of choice for evaluating the patients with lung mass. It can provide most of information about the primary tumor, mediastinal & hilar nodes and distant organ metastasis, resulting in accurate clinical tumor staging and treatment planning. Low dose chest CT scan is the investigation used for lung cancer screening, not for diagnosis because it is a non-contrast study.

2. Which one of the followings can be easily detected by using the MRI over the chest CT scan?
  - (A) Pleural effusion
  - (B) Brachial plexus involvement
  - (C) Low metabolic type lung cancer
  - (D) Metastatic mediastinal lymph nodes
  - (E) Contralateral metastatic lung nodule

Answer: (B)

MRI is better than CT scan for evaluating the mediastinal, pleural, chest wall, spinal, brachial plexus or vascular invasion because of the excellent tissue contrast.

3. Which one of the followings has the most benefit in lung cancer screening with low dose CT?
  - (A) Non-smokers
  - (B) Current smokers
  - (C) Young adult smokers
  - (D) Second hand smokers
  - (E) Former heavy smokers

Answer: (E)

Former heavy smokers have been classified to be the high-risk group proposed by the NLST in the reduction of lung cancer mortality rate > 20% for lung cancer screening.

4. According to the 2015 WHO classification of lung tumors, which term is discontinued?
- (A) Erdheim-Chester disease
  - (B) Bronchioloalveolar carcinoma
  - (C) Basaloid squamous cell carcinoma
  - (D) Atypical adenomatous hyperplasia
  - (E) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Answer: (B)

The terms bronchioloalveolar carcinoma and mixed subtype adenocarcinoma are discontinued in the 2015 WHO classification. The other choices are currently used including Erdheim-Chester disease which is newly added since it has become well characterized.

5. Which one is correct for minimally invasive adenocarcinoma (MIA)?
- (A) Its size is less than 5 cm in diameter
  - (B) The major cell type is mucin-producing
  - (C) Tumor necrosis is one of common features
  - (D) Spreads through air spaces are occasionally seen
  - (E) Invasive component could be any histologic subtype other than a lepidic pattern

Answer: (E)

Minimally invasive adenocarcinoma (MIA) is defined as a solitary adenocarcinoma with predominantly lepidic growth ( $\leq 3$  cm). Its cell type is mostly nonmucinous (type II pneumocyte or Clara cell). Presence of tumor necrosis and spreads through air spaces are exclusion criteria. Invasive component could be any histologic subtype other than a lepidic pattern (such as acinar, papillary, micropapillary, solid, colloid or fetal).

6. According to the 2015 WHO classification of lung tumors, which is the most appropriate diagnosis for the poorly differentiated carcinoma without evidence of glandular differentiation and keratinization that reveals immunostaining profile as follows; TTF-1(+), Napsin A(+), p63(-), CK5/6(-)?
- (A) Large cell carcinoma
  - (B) Solid adenocarcinoma
  - (C) Undifferentiated carcinoma
  - (D) Poorly differentiated adenocarcinoma
  - (E) Nonkeratinizing squamous cell carcinoma

Answer: (B)

The poorly differentiated carcinoma lacking evidence of glandular differentiation is proven by immunohistochemistry (IHC) to express “adenocarcinoma markers” (such as TTF-1 and/or Napsin A), it is diagnosed as a solid adenocarcinoma. The poorly differentiated carcinoma lacking evidence of squamous differentiation is proven by IHC to express “squamous cell carcinoma (SQCC) markers” (such as p40, CK5/6 or p63), it is diagnosed as nonkeratinizing SQCC. Large cell carcinoma can only be diagnosed in a resected tumor specimen. It is the poorly differentiated carcinoma lacking microscopic and immunohistochemical evidence of glandular, squamous and neuroendocrine differentiation. Undifferentiated carcinoma and poorly differentiated adenocarcinoma are not diagnostic terms in the 2015 WHO classification.

7. Which one is strongly associated with *EGFR*-mutated lung adenocarcinoma?

- (A) Caucasians
- (B) Male gender
- (C) Heavy smoking
- (D) Hobnail cell type
- (E) Acinar histologic pattern

Answer: (D)

*EGFR*-mutated adenocarcinoma is characterized by East-Asian ethnicity, female gender, non/light-smoking history and typically shows a hobnail cell type. Adenocarcinoma with a micropapillary pattern is associated with a higher frequency of *EGFR* mutation than tumor without this pattern.

8. Which one is a treatment of choice for surgical resection in patients diagnosed T1bN0M0 NSCLC at right middle lobe and having % predicted FEV1 90%?

- (A) Wedge resection with systematic LN sampling
- (B) Segmentectomy with systematic LN dissection
- (C) Lobectomy with systematic LN dissection
- (D) Lobectomy with lobe-specific LN dissection
- (E) Pneumonectomy with systematic LN sampling

Answer: (C)

According to NCCN guideline 2018 and third ACCP guideline, lobectomy with systematic LN dissection is the treatment of choice for early stage NSCLC patients who are medically operable and low risk for postoperative pulmonary complication. Sublobar resection (wedge resection or segmentectomy) can be performed in poor pulmonary reserved patients (% predicted FEV1 < 80% or FEV1 < 1.5 liters). Lobe-specific LN dissection can be performed in early disease but can not be applied if tumor located at right middle lobe because of no specific lymphatic pattern.

9. Which one of the following is not contraindication for surgery in N2 disease?

- (A) Bulky N2 disease
- (B) Multiple matted N2 disease



- (C) Matted node continuous with the primary tumor
- (D) Encase mediastinal vessels or airway
- (E) Single N2 disease

Answer: (E)

The contraindications to surgery for N2 disease included a large (> 3–5 cm) “bulky” N2, multiple matted N2 that cannot be individually discerned, continuous with the primary tumor and encase mediastinal vessels or airways, or unfitted patients. Single N2 disease is not contraindication for surgery in N2 disease.

10. Which one of the following is true about induction therapy in resectable N2 disease?
- (A) Surgery can be performed in patients with  $T_{3-4}N_{0-2}M_0$  or  $T_{1-3}N_3M_0$ , resectable with R0 resection
  - (B) Restaging of lung and mediastinum after induction therapy is not necessary
  - (C) Repeated mediastinoscopy can be performed for restaging after induction therapy with very high accuracy
  - (D) VATS can be safely performed in selected cases and similar overall survival or disease-free survival to open thoracotomy approach
  - (E) If incidental (occult) N2 disease was found at surgical resection despite fully preoperative staging methods, complete resection with SLND should be avoided.

Answer: (D)

Surgery is not recommended in N3 disease (at least stage IIIB). Restaging of lung and mediastinum after induction therapy is necessary to assess response, confirm resectability and exclude disease progression. The false negative of repeated mediastinoscopy for restaging of the mediastinum after induction therapy is high (22%), therefore, other procedures such as EBUS-TBNA have been recommended first.

11. Which one of the following is true about SBRT in early stage NSCLC?
- (A) Patients with operative mortality <1.5%, SBRT is not recommended as an alternative to surgery outside of a clinical trial
  - (B) SBRT should not be delivered exceed 5 fractions in high risk patients
  - (C) The contraindication is tumor >5 cm in largest diameter
  - (D) Tissue diagnosis procedure must be performed before SBRT without exception
  - (E) The recent meta-analysis demonstrated that stage I-II NSCLC patients with SBRT achieved inferior locoregional and distant control survival compared with surgery

Answer: (A)

For high risk patients, SBRT should be delivered in 6–15 fraction. Tumor size >5 cm with an acceptable therapeutic ratio, SBRT is an appropriate option. Tissue diag-

nosis procedure is recommended, but in patients who refuse a biopsy or who are thought to be at prohibitive risk of biopsy, discussion in a multidisciplinary manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lung lesion based on tumor, patient, and environmental factors are recommended. The recent meta-analysis demonstrated that stage I-II NSCLC patients with SBRT achieved superior OS, DFS, local, regional, locoregional, and distant control survival, compared with surgery.

12. Which one of the following is not T4 definition according to eighth edition of TNM staging system issued by IASLC?
- (A) Tumor >7 cm in largest diameter
  - (B) Separate tumor nodule(s) in a different ipsilateral lobe
  - (C) Tumor invade diaphragm, mediastinum and trachea
  - (D) Tumor invade phrenic nerve or recurrent laryngeal nerve
  - (E) Tumor invade esophagus or vertebral body

Answer: (D)

Tumor invade phrenic nerve was defined as T3 according to eighth edition of TNM staging system issued by IASLC.

13. What is the biomarker for first-line advanced non-small cell lung cancer therapy?
- (A) PD-1
  - (B) PD-L1
  - (C) PD-L2
  - (D) CD4
  - (E) CD8

Answer: (B)

According to Keynote-024 trial, patients with metastatic NSCLC having high PD-L1 expression and received pembrolizumab had a statistically significant improvement in PFS and OS. PD-L1 status should be a new predictive biomarker in NSCLC. While other markers do not correlate with the clinical outcome.

14. What of the following is the life-threatening adverse event from EGFR-TKI?
- (A) Interstitial lung disease
  - (B) Diarrhea
  - (C) Mucositis
  - (D) Transaminitis
  - (E) Skin rash

Answer: (A)

Interstitial lung disease (ILD) is the life-threatening adverse event from using EGFR-TKI. Whenever ILD is suspected or diagnosis is confirmed, EGFR-TKI should be discontinued, and systemic steroids administration should be considered. Patients with diarrhea, paronychia, hepatotoxicity and skin rash have no need to treat with systemic steroids.

15. What is the most common resistance mechanism after third generation EGFR-TKI in T790 M positive advanced NSCLC?
- (A) c-Met mutation
  - (B) c-797S mutation
  - (C) K-Ras mutation
  - (D) HGF mutation
  - (E) T790 M mutation

Answer: (B)

C-797S mutation is a major mechanism for resistance to T790 M-targeting EGFR inhibitors.

16. Which one of the following is common clinical characteristic of EML4-ALK fusion lung cancer?
- (A) Female
  - (B) Smoker
  - (C) Young age
  - (D) squamous cell carcinoma
  - (E) EGFR mutation

Answer: (C)

EML4-ALK mutant patients were associated with younger, men, adenocarcinoma, EGFR wild-type and never/light smokers compared with ALK wild-type group.

17. Which one of the following chemotherapeutic agents is not recommended for treatment in advanced stage squamous carcinoma of lung?
- (A) Cisplatin
  - (B) Docetaxel
  - (C) Etoposide
  - (D) Paclitaxel
  - (E) Pemetrexed

Answer: (E)

Pemetrexed is the only chemotherapy had shorter survival in squamous histology in multiple phase 3 trial in advanced NSCLC.

### **Clinical Case**

A 65 years male patient presented with right upper lung (RUL) nodule during yearly check-up chest X-ray. PET-CT scan was done and found hypermetabolic uptake of FDG (SUV of 15.3) of spiculated RUL nodule, size 2 × 3 × 2 cm, no significant mediastinal lymphadenopathy and no others distant metastatic lesions found. RUL lobectomy and systematic lymph node dissection was performed. The pathologic results were adenocarcinoma, size 3 cm in maximal diameter, malignant cell found at lymph node station 10 and 11. No metastatic cell found at all N2 levels. Adjuvant chemotherapy was given. One year after complete treatment, he developed bilateral multiple lung nodules.

### Questions:

1. What is the eighth edition of Clinical and pathologic TNM staging issued by IASLC?
2. What is the appropriate chemotherapy regimen for adjuvant setting?
3. Comment on the first-line therapeutic options of the above case.

### Comments:

1. According to eighth edition of TNM staging issued by IASLC, this patient had T1c, N0, M0, stage IA3 for clinical staging and T1c, N0, M0 IIB for pathological staging. The appropriate treatment for clinical stage IA3 is surgical treatment. RUL lobectomy with systematic lymph node dissection or sampling should be performed in this patient. After surgery, the pathological stage was stage IIB with metastatic N1 disease. Adjuvant chemotherapy should be considered.
2. According to ESMO clinical practice guideline 2017 and NCCN guideline 2018, adjuvant therapy with a two-drug combination with cisplatin should be offered to patient with resected stage II and III NSCLC. The most frequently studies regimen is cisplatin/vinorelbine, but other agents such as docetaxel, gemcitabine, pemetrexed, and etoposide can be considered.
3. For metastatic disease or tumor recurrence, molecular testing with *EGFR* mutation, *ALK*, *ROS1*, *BRAF*, and PD-L1, either from previous surgical specimen or new biopsy of metastatic lesion, should be performed. *EGFR* tyrosine kinase inhibitor can be used if *EGFR* testing shown exon 19 deletions, p.L858R point mutation in axon 21. Alectinib or Crizotinib can be used if *ALK* testing shown an *ALK* rearrangements. FDA-approved IHC with D5F3 CDx Assay for detecting *ALK* rearrangement can be utilized as a stand-alone test, not requiring confirmation by FISH. The presence of a *ROS1* rearrangement or *BRAF* point mutation is associated with responsiveness to oral *ROS1* TKIs or oral inhibitor of *BRAF* and *MEK*. The checkpoint inhibitor therapy can be used if presenting of PD-L1 expression. If molecular testing is not available or all negative results, a doublet with cisplatin-based chemotherapy should be considered. There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with non-squamous histology, in comparison to cisplatin/gemcitabine.

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# Chapter 10

## Small Cell Lung Cancer



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**Abstract** Small cell lung cancer (SCLC) is a disease of the smoking population. The incidence decreased to approximately 13% of all lung cancer because of a decrease in the number of cigarette smokers. The majority of patients are diagnosed with advanced stage due to the aggressive behavior. SCLC is highly responsive to combination chemotherapy however the survival time seems dismal because of the high rate of relapsing disease. Many targeted therapy are still ineffective. The immunotherapy might be effective in SCLC but there are only limited data have been reported.

**Keywords** Small cell lung cancer · Neuroendocrine tumor · Prophylactic cranial irradiation

### Abbreviations

CT	Computed Tomography
GI	Gastrointestinal
IASLC	International Association Study of Lung Cancer
JCOG	Japan Clinical Oncology Group
LCNEC	Large Cell Neuroendocrine Carcinoma

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NET	Neuroendocrine Tumor
OS	Overall Survival
PCI	Prophylactic Cranial Irradiation
PET	Positron Emission Tomography
RCT	Randomized Controlled Trial
SCLC	Small Cell Lung Cancer
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
TRT	Thoracic Radiotherapy

## 10.1 Introduction

Small cell lung cancer(SCLC) is classified as a neuroendocrine carcinoma. Patients with SCLC are usually diagnosed with advanced stage at presentation because it has aggressive behavior, rapid growth and early spread to distant sites. This chapter will discuss on epidemiology, pathology, stage of disease, diagnostic work up and treatment modalities.

## 10.2 Epidemiology

### 10.2.1 Incidence and Prevalence

Nearly all patients with small cell lung cancer (SCLC) were or active smokers. SCLC, the incidence has decreased from 25% of all lung cancers in 1993 to approximately 10–15% in 2017 [1–3]. This could be explained by the decrease in prevalence of smokers because smoking remains the predominant risk factor for this disease [1]. The prognosis and therapeutic options in SCLC are still limited and the median survival of patients with advanced SCLC with chemotherapy is between 8 and 10 months [4–11].

### 10.2.2 Genetics in SCLC

There are many studies analyzing SCLC tissue to discover a somatic genetic alteration in SCLC as shown in Table 10.1 [12]. Nearly all SCLCs (75%–90%) show loss of the prominent tumor suppressor protein 53 (TP53), Retinoblastoma 1 (RB1), RASSF1 and FHIT which are poor therapeutic targets.



**Table 10.1** Genetic alteration in Small-Cell Lung Cancer

Gene	Alterations (Frequency)
TP53	Missense mutation, deletion (75–90%)
RB1	Deletion, complex genomic translocations (100%)
RASSF1	Loss (>90%)
FHIT	Loss (80%)
MYC	Overexpression, gain of function (20%)
cKit	Overexpression
PARP1	Overexpression
PTEN	Deletion (5%)
FGFR1	Amplification (<10%)
c-MET	Amplification, Overexpression

Modified from Kahnert et al. [12]

### 10.3 Diagnosis and Staging

The investigations and staging workup for SCLC include, history taking, physical examination, CT, PET or PET/CT, MRI, bone scan, bone marrow aspiration or biopsy which are routinely performed to identify metastasis.

The role of PET or PET/CT scan for initial staging of SCLC has been evaluated in many studies. In summary, it can provide 16% up-stage disease and also 11% of down-stage disease, compared with conventional imaging, which influence the decision making process, approximately 30% change in treatment [13]. Moreover, current study found that patients with limited-stage evaluated by PET achieved an improved disease control and survival comparing with non-PET scan. The OS was 32 months in PET-staged patients and 17 months in non-PET-staged patients ( $p=0.03$ ). The better intrathoracic disease evaluation may explain these findings [14]. Therefore, in patients with clinically limited-stage SCLC, PET scan is suggested [13].

In the past, SCLC staging was classified into two stages; limited-stage and extensive-stage; however, now a day, it has been inconsistently defined and used. The TNM classification and stage grouping should be applied to SCLC because of presenting significance for prognosis of SCLC and has the advantage of providing a uniform detailed classification of tumor spread [15–17]. Limited-stage includes any T, any N, M0, that be safe for definite radiotherapy, except T3-T4 due to multiple lung nodules or lesions and LNs that are too large that do not tolerate the definite radiotherapy. Extensive-stage includes any T, any N, M1a-c or T3-T4 due to multiple lung nodules.

## 10.4 Pathology

SCLC has been grouped together with carcinoid tumor and large cell neuroendocrine carcinoma (LCNEC) under pulmonary neuroendocrine tumors (Lung NETs) in 2015 WHO classification [18]. SCLC is a poorly differentiated epithelial tumor of small cells with scant cytoplasm whereas LCNEC is composed of pleomorphic cells with variable amount of granular eosinophilic cytoplasm and round-to-oval vesicular nuclei. LCNEC and SCLC were designated as high-grade full-blown carcinomas with poor prognosis and no significant differences in survival between them (Table 10.2) [19].

### 10.4.1 Gross Pathology

SCLCs are usually white-tan, soft, friable perihilar tumors with massive necrosis and often nodal metastasis. They typically spread along bronchi in a submucosal and circumferential fashion with frequently extensive lymphatic invasion.

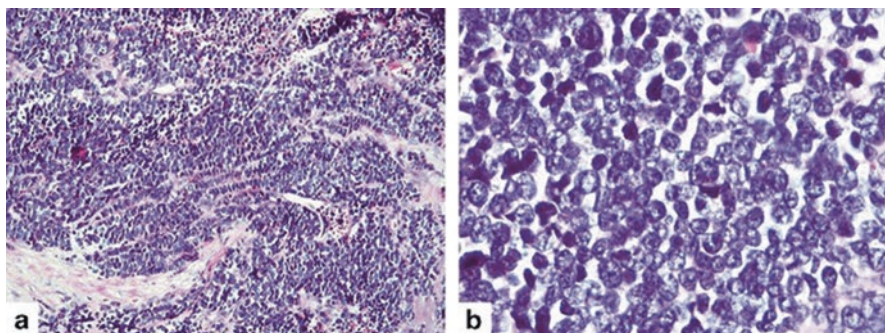
### 10.4.2 Histopathology

The tumors exhibit a wide spectrum of architectures including nest, trabeculae, strands, and rosette formation. Single cell fashion or sheet-like growths without typical neuroendocrine morphology are also common as shown in Fig. 10.1. SCLC cells usually have round, ovoid or spindle nuclei and scant cytoplasm. Characteristic

**Table 10.2** 2015 WHO classification of pulmonary neuroendocrine tumors

Small cell carcinoma
Combined small cell carcinoma
Large cell neuroendocrine carcinoma
Combined large cell neuroendocrine carcinoma
Carcinoid tumors
Typical carcinoid tumor
Atypical carcinoid tumor
Preinvasive lesion
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Modified from Travis et al. [19]  
*SCLC* small cell lung carcinoma



**Fig. 10.1** Small cell carcinoma (a) Solid sheets and occasional trabeculae of densely packed malignant cells showing scant cytoplasm, finely granular chromatin (Hematoxylin and eosin 200 $\times$ ). (b) Neoplastic cells show round nuclei with finely granular chromatin, absence of nucleoli and scant cytoplasm. High mitotic rate is typical feature (Hematoxylin and eosin 400 $\times$ )

cytologic features include ill-defined cytoplasmic borders, finely granular nuclear chromatin, absent or inconspicuous nucleoli, and prominent nuclear molding. Mitotic rate is high. The diagnosis can be confirmed by using the panel of IHC including chromogranin A, synaptophysin, and CD56. Moreover, using mitotic index (Ki-67) and retinoblastoma protein is applied for prognostic and predictive markers between well differentiated and poorly differentiated lung NETs [20].

## 10.5 Clinical Presentation

SCLC is characterized by more aggressive behavior and early development of widespread metastases. The proportion of new cases in limited stage SCLC is approximately 40%. When compared with NSCLC, SCLC is more responsive to chemotherapy and radiation initially but relapse occurs quickly, with a 5-year survival rate < 10% [1]. Brain metastases are common in SCLC, approximately 10–14% of SCLC patients have brain metastases at the time of diagnosis [21].

Paraneoplastic syndromes such as Cushing syndrome, carcinoid syndrome, Lambert-Eaton myasthenia syndrome, dermatomyositis, thrombocytosis or thromboembolism are more commonly presentations in SCLC than those in NSCLC, especially in Cushing syndrome (up to 50% of SCLCs) or SIADH (Syndrome of Inappropriate Antidiuretic Hormone, up to 45%) [22]. Other clinical presentations in NSCLC also can present in SCLC such as chronic cough, hemoptysis, or chest pain. Because SCLC is usually located at the central part of the respiratory airway, superior vena cava syndrome is also more common than in NSCLC.

## 10.6 Treatment Approaches

Treatment modalities of SCLC include chemotherapy, radiotherapy, radiosurgery and surgery. Chemotherapy and radiotherapy have a primary role, however, for curative-intent, especially in limited-disease; surgery or radiosurgery should be considered.

### 10.6.1 Surgery

Radiotherapy and chemotherapy are primary treatments of SCLC, however, surgery may have a role in early disease. Recent study using propensity matching analysis compared OS between surgical treatment (2,619 patients) and chemotherapy-based non-surgical treatment (27,375 patients) of stage I-III SCLC from National Cancer Database found that surgery was associated with longer survival for Stage I (median OS 38.6 months vs. 22.9 months, HR 0.62 95%CI 0.57-0.69), but survival differences were attenuated for Stage II (median OS 23.4 months vs. 20.7 months, HR 0.84 95%CI 0.70-1.01) and IIIA (median OS 21.7 vs. 16.0 months, HR 0.71 95%CI 0.60-0.83). In analyses by T and N stage, longer OS was observed in resected T3/T4 N0 patients (median OS 33.0 vs. 16.8 months,  $p=0.008$ ) and node positivity (N1+ 24.4 vs. 18.3 months  $p=0.03$ ; N2+ 20.1 vs. 14.6 months  $p=0.007$ ). In the subgroup analysis of stage I/II patients, patients underwent lobectomy with adjuvant chemotherapy was associated with significantly longer survival (median OS 48.6 vs. 28.7 months,  $p<0.0001$ ) than those with CCRT without surgery. They concluded that surgical resection is associated with significantly longer survival for early SCLC [23]. A large population data-base, US population-based database from 1988 to 2002 with 14,179 SCLC patients and 863 (6.1%) of these who underwent surgery were analyzed. Surgical was more commonly performed in limited-disease and had longer survival than in the non-surgical group. Patients with localized disease underwent lobectomy had a median survival of 65 months and a 5-year OS of 52.6% whereas patients who had regional disease had a median survival of 25 months and a 5-year OS rate of 31.8%. Only N2 disease patients received a benefit from adjuvant radiotherapy [24]. Another larger database, The National Cancer Institute Surveillance Epidemiology and End Results (SEER) database from 1988 to 2004 with 1,560 stage I SCLC patients was analyzed to evaluate outcomes between surgical and non-surgical groups. They found that the 5 year survival in patients who underwent lobectomy with postoperative radiotherapy was comparable with those without postoperative radiotherapy (50% versus 57%, respectively) [25]. The ACCP guideline 2013 and NCCN guideline 2017 summarized that surgical resection is recommended in patients with clinical stage I (T1-T2, N0, M0 disease) SCLC after being fully evaluated in distant metastasis and invasive mediastinal staging (head MRI/CT and PET or abdominal CT plus bone scan) and these patients should receive platinum-based adjuvant chemotherapy if pathologic nodal negative, and

concurrent chemotherapy with mediastinal radiotherapy if nodal positive. Other indications for surgery in SCLC include 1) solitary pulmonary nodule cytologically diagnosed as SCLC (small cytologic samples may be typical or atypical carcinoid tumors; 2) having combined histology tumors (SCLC and NSCLC); 3) persistent local disease after chemoradiotherapy (possible NSCLC component) if operability and resectability; and 4) new metachronous tumor in small-cell survivor (after complete re-staging) that may be a new NSCLC [3, 26].

### **10.6.2 Chemo-Radiotherapy**

Two meta-analysis confirmed addition of thoracic radiotherapy improves local control and OS compared with combination chemotherapy alone. The first 11 randomized trials demonstrated absolute increase in OS of 5.4% at 2-years survival [27]. The second 13 randomized trials demonstrated absolute increase in OS of 5.4% from 15% to 20.4% at 3-years [28]. Cisplatin-etoposide concurrent with radiotherapy is more effective than sequential chemo-radiotherapy (median survival of 27.2 months VS 19.7 months, 5-year survival of 23.7% VS 18.3%) [29]. One phase III trial reported superior 5-year OS with twice-daily radiotherapy (1.5 Gy twice-daily, 30 fraction) compared with once-daily (1.8 Gy, 25 fractions) of 26% versus 16% [30]. The optimal timing of the concurrent radiotherapy should be initiated as early as possible. Two meta-analyses showed improvement of 2-year survival with early chemo-radiotherapy compared with late chemo-radiotherapy [31, 32]. On the other hand, recent phase III study demonstrated that patients with limited-stage SCLC receiving late thoracic radiotherapy (TRT) (concurrent TRT start at the third cycle) seemed to be non-inferior to early radiotherapy in term of the complete response rate (late versus early; 38% vs. 36%) and less neutropenic fever [33].

TRT in the patients with extensive-stage SCLC after chemotherapy and prophylactic cranial irradiation (PCI) was assessed from retrospective study showed the median PFS 4.2 months and OS 8.3 months [34]. The data from phase III study stated that patients with extensive-stage SCLC receiving chemotherapy and PCI slightly increase 1-year survival from 28% to 33% and significant prolong 2-year OS from 3% to 13% in TRT arm without severe toxic effect [35].

### **10.6.3 Prophylactic Cranial Irradiation (PCI)**

Brain metastases developed in about 30% of patients [36]. Survival after relapse is generally poor, with a median survival of approximately 4 months. Chemotherapy does not reduce the incidence of brain metastases [37]. PCI in patients that achieve complete response (CR) or near CR in Limited-stage SCLC showed a significant decrease in the incidence of brain metastases at 3 years (33.3% VS 58.6%) [38, 39] and improved quality of life and 5-year survival (22–26%) [40]. Total dose of PCI

24–36 Gy, with once-daily or twice-daily fractions equal to 2–3 Gy/day; PCI and concomitant chemotherapy can increase toxicity and should be avoided [21]. In extensive stage, PCI significantly decrease the risk of symptomatic brain metastases (40.4–14.6% at 1 year) and improved the 1-year survival (13.3–27.1%) with median OS 5.42 and 6.74 months in the PCI arm [41]. In 2015, the study from Japan also investigated the effect of PCI in Limited-SCLC, if SBRT is available and patients can be followed-up with MRI every 3 months, PCI may be not necessary [42]. However, the brain imaging is not part of standard follow-up examination. The results from recent systematic review and meta-analysis indicated that PCI decrease brain metastasis and improve survival in SCLC patients even if the elderly patients. Therefore, PCI should be taken into consideration for all patients who achieve response to first-line chemotherapy and are in a good general condition [43].

### **10.6.4 Chemotherapy**

Combination chemotherapy has been the main treatment option in extensive-stage SCLC. A meta-analysis of 19 randomized trials with a total of 4,054 patients demonstrated prolonged OS of patients receiving a cisplatin-containing regimen versus a regimen containing others alkylating agents [44]. Cisplatin-etoposide is the standard regimen for extensive-stage SCLC with high response rate 60–80%, median survival 8–10 months [4–11]. There were 3 RCTs studied in combination of cisplatin-irinotecan compared with cisplatin-etoposide in extensive-stage SCLC, the first study from Japan Clinical Oncology Group (JCOG) demonstrated improvement of response rate (67.5–84.4%), PFS (4.8–6.9 months), median survival (9.4–12.8 months) in cisplatin-irinotecan arm [9]; however, the others were not confirmed to be superior in cisplatin-irinotecan combination in terms of response rate, PFS and OS [6–8]. The randomized Phase 3 trial from Japan, limited-stage SCLC who achieved no progression after concurrent chemoradiation with cisplatin-etoposide, cisplatin-irinotecan consolidation failed to demonstrate improvement of median overall survival compared with cisplatin-etoposide consolidation (2.8 years versus 3.2 years) [45]. Cisplatin is associated with more GI adverse effects, neurotoxicity, and renal function impairment, and its administration requires a prolonged hydration, but carboplatin is associated with more myelosuppression [46]. Recently meta-analysis of individual patient data shows that carboplatin-based regimens appear to be equally effective in terms of OS, PFS, and ORR compared with cisplatin-based combinations for the first-line therapy of SCLC [47]. A randomized Phase III trial in Scandinavian countries compared an irinotecan plus carboplatin regimen with an oral etoposide plus carboplatin in extensive-stage SCLC, that demonstrated carboplatin plus irinotecan prolonged median survival (7.1–8.5 months), improved 1 year survival (24–34%) with a slightly better quality of life [48]. The increase in toxicity with an addition of a third agent (ifosfamide or paclitaxel) to cisplatin-etoposide did not improve the overall survival [49–52]. To date, no molecularly targeted agents have yielded a prolonged survival in patients with SCLCs.

In second-line chemotherapy, Patients with small-cell lung cancer (SCLC) that progress after first-line chemotherapy have a poor prognosis and the evidence of a benefit from second-line (SL) chemotherapy is limited depend on the response and duration of response of previous platinum base chemotherapy. If the interval of disease remission from first-line chemotherapy is less than 3 months (resistant or refractory disease) the response of second-line is very poor. In case of the relapse time of disease is greater than 3 months (sensitive disease) the response of second-line will be expected around 25%. A meta-analysis in 21 studies published between 1984 and 2011 demonstrated the response rate to second-line treatment is 27.7% in sensitive disease and 17.9% in refractory disease. The median survival time was 7.7 months and 5.4 months respectively [53].

Relapse SCLC patients who received oral topotecan experienced an improved median survival time compared with the best supportive care alone (25.9 weeks versus 13.9 weeks)  $P=0.01$  [54]. Cyclophosphamide, doxorubicin, and vincristine (CAV) was as effective as topotecan in second line therapy with median survival 24.7 weeks [55]. Another randomized trial, oral topotecan demonstrated activity and tolerability similar to IV topotecan in chemotherapy-sensitive SCLC patients and offered [56] 33 weeks and 35 weeks respectively [57]. A multicenter phase III trial from Japan (JCOG0605) reported the efficacy between combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed SCLC and found that OS was significantly longer in the combination chemotherapy group (median 18.2 months, 95% CI 15.7-20.6) than in the topotecan group (12.5 months, 10.8–14.9; hazard ratio 0.67, 90% CI 0.51-0.88;  $p=0.0079$ ). The adverse events such as Grade 3 or 4 febrile neutropenia, or grade 3 or 4 thrombocytopenia were not significantly different [58].

### 10.6.5 Immunotherapy

Cancer immunotherapies aim to stimulate immune responses, thereby inhibiting the tumor from escaping immune surveillance. Two well-characterized checkpoint pathways include the cytotoxic T-lymphocyte antigen-4 protein (CTLA-4) and programmed cell death-1 protein receptor (PD-1) and ligand (PD-L1) pathways.

There was the phase I/II trial studied in patients with progressive SCLC who were previously treated with platinum-based chemotherapy and were not tested for PD-L1 expression, the objective response rate of nivolumab monotherapy and combination with ipilimumab were 18% and 17% and the OS were 4.4 months and 8.2 months respectively and the toxicity were manageable [59, 60]. The phase Ib trial studied in patients with SCLC prior receiving platinum-based chemotherapy, the observed objective response rate in patients who had expression of PD-L1 positivity at the 1% cut off threshold evaluated by IHC treated with pembrolizumab monotherapy was 33% and the median survival was 9.7 months [61, 62]. Phase II trial studied in the combination of ipilimumab with paclitaxel and carboplatin in two alternative regimens; 1) phased ipilimumab (placebo+paclitaxel/carboplatin

followed by ipilimumab + paclitaxel / carboplatin), 2) concurrent ipilimumab (ipilimumab+paclitaxel/carboplatin followed by placebo + paclitaxel/carboplatin) or, and placebo. The median PFS time and median OS time were 5.2, 3.9 and 5.2 months and median OS of 12.9, 9.1 and 9.9 months, respectively [63].

## 10.7 Conclusion

In summary, SCLC is an aggressive cancer. Most of patients are in the extensive stage at first presentation. Combination chemotherapy can achieve high overall response rates, but the duration of response is still short. It is important to seek effective targeted therapies to treat SCLC. Although targeted therapy drugs are widely investigated in NSCLC, currently, there are no approved for SCLC. The early phase clinical studies have demonstrated that immunotherapies targeting immune-checkpoint inhibition may improve survival. Further research on immune-checkpoint inhibition will be necessary to improved outcome in patients with SCLC.

### Key Points

- Small cell lung cancer (SCLC) is a high grade neuroendocrine tumor which related with history of smoking.
- Surgical approach is not the standard treatment due to the aggressive behavior of tumor and majority of patient were diagnosed with metastatic disease. However, surgical resection followed by platinum-based chemotherapy be considered in patients with stage I SCLC.
- Small cell lung cancer (SCLC) is the highly sensitive chemotherapy disease. Although combination chemotherapy can achieve high rate of response of tumor but the prognosis still poor due to high rate of the disease relapse.
- Prophylaxis cranial irradiation (PCI) can reduce incidence of brain metastases in both limited-stage and extensive-stage SCLC who achieve response to the initial systemic chemotherapy.
- Many targeted therapy have been studied but seem to still be ineffective.
- The immunotherapy has been proposed and might be the new hope in treatment of SCLC and have to be further explore in the future.

### Multiple-Choice Questions

1. Which is the 5-year survival of resectable of small cell lung cancer?
  - A. 10–20%
  - B. 20–30%
  - C. 30–50%
  - D. 50–70%
  - E. 70–80%

Answer: D

Surgery is not the mainstay treatment option for SCLC. In case of localized disease underwent lobectomy had median survival of 65 months and a 5-year OS of 52.6%.



2. Which is the 5-year survival of regional disease of small cell lung cancer?
- A. 10–20%
  - B. 20–30%
  - C. 30–50%
  - D. 50–70%
  - E. 70–80%

Answer: C

Radiotherapy and chemotherapy are primary treatments of SCLC. Patients with regional disease had a median survival of 25 months and 5-year OS of 31.8%.

3. Which of the following is the most common paraneoplastic syndrome in SCLC?
- A. Hypercalcemia
  - B. Cushing syndrome
  - C. Carcinoid syndrome
  - D. Paraneoplastic encephalomyelitis
  - E. Paraneoplastic cerebellar degeneration

Answer: B

The two most common paraneoplastic syndromes for SCLC are Cushing syndrome and SIADH. Humoral hypercalcemia of malignancy is the common paraneoplastic syndrome of squamous cell carcinoma.

4. A 60-year-old man presented with chronic cough and was diagnosed with limited-stage SCLC.

He has good performance status. The basic laboratory is within normal limit. What of the following is the most appropriate treatment?

- A. Cisplatin and etoposide chemotherapy
- B. Cisplatin and etoposide chemotherapy follow by thoracic radiation
- C. Cisplatin and etoposide chemotherapy with concurrent thoracic radiation
- D. Carboplatin and etoposide chemotherapy with concurrent thoracic radiation
- E. Cisplatin and etoposide chemotherapy follow by PCI if response to chemotherapy

Answer: C

The standard therapy for patients with limited stage-SCLC who still have good performance status is chemotherapy with concurrent radiation with cisplatin/etoposide.

5. A 70-year-old man with 40-pack-year smoking history presented with alteration of consciousness. MRI of brain was normal. CXR showed left hilar mass. The additional laboratory test showed Na 116 mEq/L. Otherwise blood chemistries are within normal limits. Bronchoscope with biopsy was done. Which of the following is most likely pathologic result?
- A. Lung cancer with positive EGFR mutation
  - B. Lung cancer with positive KRAS mutation

- C. Lung cancer with positive synaptophysin IHC
- D. Lung cancer with positive ALK rearrangement
- E. Neoplastic cells with positive CD117 IHC

Answer: C

SIADH is the more common paraneoplastic syndrome for SCLC than NSCLC. EGFR mutation, KRAS mutation, ALK rearrangement, and positive CD117 IHC are usually found in NSCLC, whereas, positive synaptophysin IHC is usually found in SCLC.

6. Which of the following is the most common genetic alteration in Small cell lung cancer?
- A. MYC overexpression
  - B. PTEN deletion
  - C. P53 mutation
  - D. c-MET amplification
  - E. PARP1 over expression

Answer: C

Nearly all SCLCs patient have the somatic genetic alteration and loss of the prominent tumor suppressor protein 53 (TP53).

7. Which of the following statement is correct regarding the role of prophylactic cranial irradiation (PCI) in SCLC?
- A. PCI reduce the incidence of brain metastases in limited-stage and extensive-stage SCLC
  - B. PCI improves 2-year survival in patients with extensive-stage SCLC who response to frontline chemotherapy
  - C. PCI improves 3-year survival in all patients with limited-stage SCLC
  - D. Patients who receive PCI therapy have no long-term cognitive defects
  - E. All of the above

Answer: A

PCI reduce the incidence of brain metastases in both limited and extensive stage SCLC and prolong 3-year OS for limited-stage SCLCs who achieve complete response or nearly complete response. PCI also improve 1-year for extensive-stage SCLCs who achieve response from initial combination chemotherapy.

8. A 60-year-old man diagnosed with extensive-stage SCLC presented with a bulky hilar lung mass and mediastinal LN metastases. After frontline chemotherapy, the CT scan showed nearly complete response and MRI brain showed no brain metastasis. He still has a good performance status. Which of the following is the appropriate standard of care?
- A. Clinical observe
  - B. MRI brain every 3 months
  - C. Prophylactic cranial radiation

- D. Thoracic radiation to the residual tumor
- E. Maintenance chemotherapy with oral etoposide

Answer: C

Prophylactic cranial irradiation for extensive-stage SCLC patients who achieved nearly complete response after systemic chemotherapy should be considered in patients who still have good performance status. MRI after complete treatment is not the routine surveillance imaging in SCLCs.

9. Which is the response rate of second-line chemotherapy in sensitive-disease small cell lung cancer?
- A. 10%
  - B. 15–25%
  - C. 35–45%
  - D. 50–60%
  - E. 70–80%

Answer: B

The response rate of combination platinum doublet chemotherapy in first line treatment are 60–80%, however for the second line treatment, the response rate is not very impressive even in the sensitive-disease, the response is rate only 25%.

10. A 57-year-old man without comorbid disease and good functional status presented with incidental solitary lung nodule at right upper lobe. Complete diagnostic work-up were done and found small cell lung cancer, clinical stage T1aN0M0. Which is the appropriate treatment in this patient?
- A. Chemotherapy alone
  - B. Chemotherapy and followed by radiotherapy
  - C. Lobectomy with systematic lymph node dissection
  - D. Lobectomy with systematic lymph node dissection followed by chemotherapy
  - E. Lobectomy with systematic lymph node dissection followed by chemoimmunotherapy and radiotherapy

Answer: D

According to current recommendation from ASCO, ACCP, and NCCN guideline, surgical resection followed by platinum-based adjuvant chemotherapy is recommended in patients with stage I SCLC. No previous studies have found significant advantage in the use of postoperative radiotherapy for stage I disease after R0 resection.

### Clinical Case

A 65-year-old man presented with chronic cough and weight loss. The CT scan was done showed the 4 cm left upper lobe mass with multiple lung nodule bilaterally. The MRI brain showed a single 2 cm brain metastasis without neurological symptom. The bronchoscopy and biopsy was done and diagnose to be small cell

carcinoma. The patient still do the daily life activity by himself and the blood tests for complete bold count and chemistry profiles are within normal limited.

### Question and Comments

1. Dose this patient need to start brain radiation first?
2. Which modality should be consider to treat the brain metastasis?
3. Which regimen should be first-line chemotherapy?

### Comments

1. According to NCCN guideline version 2.2018, the extensive-stage small cell lung cancer with asymptomatic brain metastasis should be start treatment with platinum-doublet systemic chemotherapy first with whole-brain radiation after completion of systemic therapy.
2. The brain metastasis in small cell lung cancer should be treated with whole-brain radiation rather than surgery or stereotactic radiotherapy/radiosurgery alone, because the patient tend to develop multiple brain metastases. However, stereotactic radiotherapy/radiosurgery could be the option in patients who underwent prophylactic cranial irradiation or whole-brain radiation.
3. The cisplatin and etoposide is the most commonly used combination. However, for the patient who are cisplatin ineligible or elderly patients, carboplatin could be used. There are meta-analysis show that carboplatin-based regimens appear to be equally effective in terms of OS, PFS, and ORR with different toxicity profiles.

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# Chapter 11

## Mesothelioma



Vangelis Karamitrousis and Nikolaos Tsoukalas

**Abstract** Malignant pleural mesothelioma (MPM) is a rare cancer, linked to asbestos exposure. The median age at diagnosis is 70 years, however it can develop in younger patients. Poor prognostic factors include: pleural disease extent, high lactate dehydrogenase, poor performance status, high platelet count, non-epithelial histology, and old age. The key inactivated driver genes are CDKN2A, NF2 and BAP1. The most common symptom is dyspnea. Pleural effusion is present in most cases of MPM, revealed by a chest X-ray. Other diagnostic procedures include ultrasonography, computed tomography, pleural effusion cytology, fluorodeoxyglucose-positron emission tomography and magnetic resonance imaging. There are three major histological subtypes of MPM: epithelioid, sarcomatoid and biphasic. Treatment of MPM includes surgery, radiotherapy and systemic therapy. Thoracoscopy aids in the diagnosis and management of MPM, especially in patients with large pleural effusions. Extrapleural pneumonectomy, pleurectomy and decortication, and palliative limited pleurectomy are the surgical operations used in the treatment of MPM. There is little benefit to adding radiotherapy to other treatments. The most common used systemic therapy regimens include a combination doublet of cisplatin, with an antifolate.

**Keywords** Mesothelioma · Asbestos · Trimodality therapy

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## Abbreviations

(c)Gy	(Centi) Gray
ACS	Active symptoms control
BAP-1	BRCA-1 associated protein-1
CDKN2A/ARF	Cyclin-dependent kinase inhibitor 2A/alternative reading frame
CEA	Carcinoembryonic antigen
CK	Cytokeratin
CT	Computer tomography
DVT	Deep venous thrombosis
ECOG	Eastern Cooperative Oncology Group
EF	Ejection fraction
FDG-PET	Fludeoxy-glucose positron emission tomography
FEV <sub>1</sub>	Forced expiratory volume in the first second
IL-1 $\beta$	Interleukin-1 $\beta$
IMRT	Intensity-modulated radiotherapy
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
MVP	Mitomycin, vinblastin, cisplatin
NF-2	Neurofibromatosis type-2
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
P/D	Pleurectomy and decortication
PPO	Predicted postoperative
PS	Performance status
RT	Radiotherapy
SV-40	Simian virus 40
TNF- $\alpha$	Tumor necrosis factor- $\alpha$
TNM	Tumor, nodal and metastasis
TTF-1	Thyroid transcription factor-1
US	Ultrasound
WT-1	Wilm's tumor gene product

### 11.1 Introduction

Mesothelioma is a rare, malignant tumor of the pleura (malignant pleural mesothelioma, MPM). It is a common disease, arising from the mesothelial cells lining the pleura [1]. Mesothelial cells form a monolayer (mesothelium) lining the serosal cavities (pleural, pericardial and peritoneal) and the organs contained within these cavities [2]. Other, less common tumors of the pleura, include solitary fibrous tumor, adenomatoid tumor, calcifying fibrous pseudotumor, and pleural desmoid tumors [3]. MPM is a resistant tumor in chemotherapy and radiotherapy, with rapid

progression and results in a median survival time of 12 months [4]. MPM extends into organs in the vicinity and disturbs functions of vital organs. It rarely metastasizes to distant organs, until it develops into a terminal stage [5]. These metastases can cause compression of heart and great vessels (leads to cardiac tamponade), superior vena cava syndrome, bone and neuropathic pain and massive pleural effusion. MPM frequently penetrates into lung parenchyma causing progressive respiratory failure [6]. Mesothelioma can also arise in the peritoneum, the pericardium or the tunica vaginalis.

## 11.2 Epidemiology and Incidence

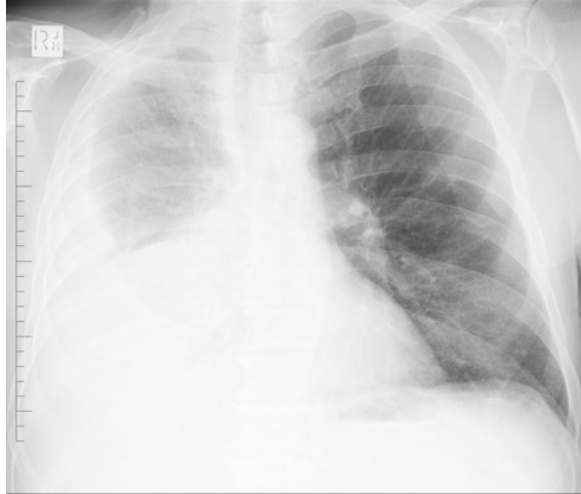
The most common cause of this tumor, is the occupational exposure to *asbestos*, in places such as mines, shipyards, cement factories etc [7]. Asbestos refers to six fibrous silicate minerals, found widely throughout the world and is divided into two categories: a serpentine form and a rodlike form.

There is a long time latency period between exposure to asbestos and development of MPM (10–30 years), so a long period of exposure to asbestos is required, in order to develop MPM. Asbestos fibers, cause chronic inflammation to the mesothelium, so this is the factor that leads to carcinogenesis, via tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ). Family members of patients with MPM, can develop this tumor in higher rates, due to secondary exposure to asbestos. Other agents that can lead to MPM formation, are mineral fibers (e.g. erionite), prior radiotherapy, thorium dioxide used for diagnostic purposes and simian virus 40 (SV-40) [8]. Nanosized particles of medical and industrial purposes could cause MPM formation [6]. Mutations of BRCA-1 associated protein-1 (*BAP1*) gene seem to lead to MPM formation, via reducing the tumor suppressor activity of BAP1 protein [9, 10]. Other mutations in critical genes, include cyclin-dependent kinase inhibitor 2A/alternative reading frame (*CDKN2A/ARF*) and neurofibromatosis type-2 (NF2). Men have poorer prognosis, because it is more likely to have occupational exposure to asbestos. MPM in young people is more aggressive, because of a greater exposure to asbestos in regard to older people who have longer survival [11, 12]. The incidence of MPM arises in 1–2 per million of the general population per year [13].

## 11.3 Clinical Manifestation and Diagnosis

There are no specific symptoms related to MPM, so the diagnosis can delay for months [14]. The most common symptom is dyspnea, which can be presented as breath shortness or exertion. Chest wall pain can also be present, due to irritation of costal nerves or tumor infiltration into chest wall. Other, less common symptoms of MPM, include fever, weight loss, sweat and performance status decline [15]. Rare

**Fig. 11.1** X-ray of right lung mesothelioma



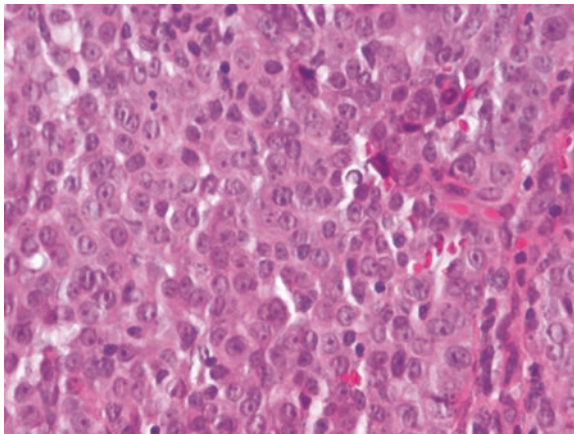
symptoms are irritative cough, phrenic nerve palsy, spontaneous pneumothorax and paraneoplastic phenomena [16]. During the physical examination can be present dullness to thorax percussion and decreased breath sounds. Thrombocytosis is a relatively common laboratory sign, whereas other laboratory abnormalities are not present [17]. Pleural effusion is present in most cases of MPM, revealed by a chest X-ray (Fig. 11.1). Differential diagnosis of the infusion includes pneumonia, tuberculosis, trauma and venous congestion.

Thoracentesis relieves the patient's symptoms but a cytologic analysis is not reliable. Computer tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) can be used to obtain further support for suspected diagnosis and assess the extent of the disease [18]. A thorascopic biopsy is often required and if the tumour is resectable, this can be during thoracotomy [19]. Prognostic factors include performance status, presence of chest pain, age, histological type and platelet count. Bad performance status, elevated white blood count, male gender and sarcomatous histological type of MPM, are associated with poorer prognosis [20]. Pain and appetite loss, are independent prognostic factors [21].

## 11.4 Histological and Molecular Characteristics – Biomarkers

There are 4 recognised subtypes of MPM: epithelioid (Fig. 11.2), sarcomatous, mixed and desmoplastic [22]. Epithelioid subtype is the most common and has better prognosis than the other subtypes of MPM. Differential diagnosis should be held with metastatic lung adenocarcinoma, non-small cell lung cancer (NSCLC) and mesothelial hyperplasia. There are antigens expressed by the mesothelial cells, such

**Fig. 11.2** Epithelioid mesothelioma



as calretinin, Wilm's tumor gene product (WT-1), mesothelin, cytokeratin (CK) 5/6, thrombomodulin, podoplanin (D2-40), HBME-1 antigen etc. Biomarkers expressed by carcinoid cells, include carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF-1), Leu-M1 (CD15), Ber-EP4, B72.3, BG-8, napsin-A. Calretinin, WT-1 and D2-40, have great specificity for MPM. Sarcomatoid type cells, express cytokeratins, vimentin and smooth muscle markers. However, there are CK-negative sarcomatoid mesotheliomas. Two positive (eg. CK 5/6, calretinin) and two negative (eg. CEA, TTF-1) markers, should be used to distinguish between MPM and NSCLC. Definite diagnosis of MPM is carried out by recognising fat or stromal tissue invasion of the tumor cells. When tissue invasion cannot be identified, the lesion is characterized as atypical mesothelial proliferation. Biomarkers that can be used in the diagnosis of MPM, are mesothelin, CA125, osteopontin and megakaryocyte potentiating factor (MPF), with poor sensitivity [23]. Circulating fibrinogen could also be a prognostic and predictive biomarker in MPM [24].

## 11.5 Staging

The staging system provides an estimate of the prognosis, and an assessment if the tumor is potentially resectable. The tumor, nodal, and metastasis (TNM) staging system, is often used (Tables 11.1 and 11.2). Patients with suspected or confirmed MPM diagnosis should be assessed for therapeutic planning with CT of the thorax and abdomen. US or CT can be used to guide biopsy and drainage of pleural effusion. New-generation spiral CT should be used on MPM imaging, because enhances definition and interpretation of lesions, due to vasculature defining. Fludeoxyglucose positron emission tomography (FDG-PET) is a more sensitive modality than CT to detect possible lymph node involvement and distant metastatic disease,

**Table 11.1** The TNM staging system of MPM [8]:

<b>TNM Description</b>			
Primary tumor			
Tx	Tumor cannot be assessed		
T0	No evidence of tumor		
T1A	No involvement of the visceral pleura		
T1B	Tumor also involving the visceral pleura		
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: involvement of diaphragmatic muscle; extension of tumor from visceral pleura into the underlying pulmonary parenchyma.		
T3	Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: involvement of the endothoracic fascia; extension into the mediastinal fat; solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall; nontransmural involvement of the pericardium.		
T4	Locally advanced, technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction; direct transdiaphragmatic extension of tumor to the peritoneum; direct extension of tumor to the contralateral pleura; direct extension of tumor to mediastinal organs; direct extension of tumor into the spine; tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium.		
Regional lymph nodes			
Nx	Regional lymph nodes cannot be assessed		
No	No regional lymph node metastases		
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes		
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary and peridiaphragmatic nodes		
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes.		
Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis present		
<b>Anatomic stage/Prognostic groups</b>			
Stage	T	N	M
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

**Table 11.2** Anatomic stage/Prognostic groups of MPM [8]

<b>TNM Description</b>			
Primary tumor			
Tx	Tumor cannot be assessed		
T0	No evidence of tumor		
T1A	No involvement of the visceral pleura		
T1B	Tumor also involving the visceral pleura		
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: involvement of diaphragmatic muscle; extension of tumor from visceral pleura into the underlying pulmonary parenchyma.		
T3	Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: involvement of the endothoracic fascia; extension into the mediastinal fat; solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall; nontransmural involvement of the pericardium.		
T4	Locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction; direct transdiaphragmatic extension of tumor to the peritoneum; direct extension of tumor to the contralateral pleura; direct extension of tumor to mediastinal organs; direct extension of tumor into the spine; tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium.		
Regional lymph nodes			
Nx	Regional lymph nodes cannot be assessed		
No	No regional lymph node metastases		
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes		
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary and peridiaphragmatic nodes		
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes.		
Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis present		
<b>Anatomic stage/Prognostic groups</b>			
Stage	T	N	M
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

and should be performed when the presence of disease in these sites will influence a management plan. FDG-PET-CT should be used in preference to FDG-PET according to availability. MRI with gadolinium enhancement can be useful where it is important to delineate tumour extension in the diaphragm, endothoracic fascia, chest wall or through iatrogenic tumour seeding [23].

## 11.6 Surgical Treatment

Thoracoscopy aids in the diagnosis and management of MPM, especially in patients with large pleural effusions. The surgeon is able to directly visualize the entire thorax space, visceral and parietal pleura and chest wall. Mediastinal structures (pericardium and mediastinal lymph nodes) can be directly evaluated to aid in determining the extent of future resection. Diaphragm can be inspected to determine the extent of disease. If diaphragmatic involvement occurs, laparoscopy can be helpful [26]. Biopsies of abnormal pleura can be performed directly. If contralateral thoracic involvement of MPM is suspected, thoracoscopy can confirm the diagnosis. After determining the extent of disease, suitability for resection must be determined and the type of resection must be decided. Extrapleural pneumonectomy (EPP), pleurectomy and decortication (P/D), and palliative limited pleurectomy are the surgical operations used in the treatment of MPM. Normal kidney and hepatic function and a Karnofsky performance status greater than 70 is required.

Additionally, the patients' room air  $P_{CO_2}$  must be less than 45 mm Hg,  $P_{O_2}$  greater than 65 mm Hg, and an ejection fraction (EF) of 45% or greater. A forced expiratory volume in the first second ( $FEV_1$ ) greater than 2 L or a predicted postoperative (PPO)  $FEV_1$  of greater than 800 mL, is also required. Patients with PPO  $FEV_1$  of less than 800 mL may be candidates for P/D rather than EPP [25]. Aim of surgery is to achieve maximum cytoreduction of the tumor (R1 resection). Surgical therapy remains the foundation of potential curative treatment for MPM. The secondary objective of surgery is to improve symptoms (evacuation of the pleural effusion and pulmonary decortication of an entrapped lung), which improves pain related to chest wall invasion of the MPM [27, 28]. The decision to perform EPP or P/D is dependent on several factors, such as the bulk of disease at the time of surgery and should be made by thoracic surgeons who are experienced in managing MPM. If minimal disease is encountered (T1) then P/D is preferable. In patients with visceral pleura involvement, EPP is appropriate for complete resection. EPP can cause pulmonary hypertension and right heart strain, so echocardiogram is used to assess cardiac function. Additionally, duplex imaging of lower extremities can assess in the diagnosis of deep venous thrombosis (DVT). These patients must take anticoagulant therapy, in order to prevent the pulmonary embolism. If the patient has diffuse disease, including chest wall involvement, EPP will leave the patient with gross residual disease and is not appropriate for this case. Therefore, the decision to perform EPP or P/D should be an intraoperative choice depending on the magnitude of disease [8].



## 11.7 Chemotherapy

Chemotherapy is used to reduce disease related symptoms, maintain or improve quality of life, and extend overall survival (OS). Candidates, should be ambulatory (ie, an Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 0 to 2 or a Karnofsky PS of  $\geq 70$ ), have adequate organ function, and not significant co-morbidities. Phase III trials have shown that the best chemotherapeutic combination for the first-line treatment of MPM is a platinum agent (cisplatin or carboplatin) with antifolate, such as pemetrexed or raltitrexed.

Combination of these agents, shows superior overall response rate (ORR), progression free survival (PFS), and overall survival (OS), contrary to cisplatin alone. In Vongelzang's phase III trial compared cisplatin vs cisplatin/pemetrexed for 456 patients. For cisplatin alone, the ORR was 16,7% and the PFS was 3,9 months, whereas for the combination cisplatin/pemetrexed, the ORR was 41,3% and the PFS was 5,7 months [29]. In Van Meerbeek's phase III trials, compared cisplatin vs cisplatin/raltitrexed for 250 patients. For cisplatin alone the ORR was 13,6% and the PFS was 4 months, whereas for the combination cisplatin/raltitrexed the ORR was 23,6% and the PFS 5,3 months [30]. In Santoro's phase III trial, compared the combinations of cisplatin/pemetrexed and carboplatin/pemetrexed for 1704 patients. For the combination of cisplatin/pemetrexed the ORR was 26,3% and the PFS was 7 months, whereas for the combination of carboplatin/pemetrexed, the ORR was 21,7% and the PFS was 6,9 months [31]. Cisplatin or carboplatin in combination with pemetrexed have similar efficacy, and carboplatin may be substituted for cisplatin in patients who have a relative or absolute contraindication to cisplatin. Active symptoms control (ASC) includes steroids, analgesic drugs, bronchodilators and palliative radiotherapy. Addition of mitomycin, vinblastine and cisplatin (MVP) with or without vinorelbine, shows no significant difference in OS [32]. There are no sufficient data for second-line therapy in MPM. Vinorelbine plus carboplatin and gemcitabine plus cisplatin or carboplatin, show good results in this case [33, 34]. Preoperative chemotherapy is a reasonable approach in some patients with resectable MPM, using the combinations of cisplatin/pemetrexed or carboplatin/gemcitabine followed by EPP and radiotherapy (RT) [35, 36].

## 11.8 Radiotherapy

RT in MPM is used for the local control of disease, since mesothelial cells are sensitive in radiation. The target is the preoperative extent of the pleural space, which is large, irregular, and close to radiosensitive organs (lungs, heart, and liver). The role of RT is used as an integral part of trimodality therapy for early-stage disease and in the palliation of pain in locally advanced/metastatic disease.

In the first case, RT is used in doses of 4500–5040 centigray (cGy) (in 180-cGy fractions) over 5 weeks in the postsurgical setting. In order to relieve the symptoms

of the disease, such as pain and dyspnea, short courses are used (e.g. 300 cGy  $\times$  10 fractions). After EPP, radiation therapy must be given in high doses (54Gy) for better results [37]. Intensity-modulated radiotherapy (IMRT) has the flexibility to deliver dose distributions that conform to complicated convex and concave target volumes, while minimizing dose to critical structures in proximity [8]. IMRT after P/D has good results in dose <40Gy [38].

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# Chapter 12

## Epithelial Thymic Neoplasms



**Mayndra Mychelle Landgraf, Daiane Pereira Guimarães, Hakaru Tadokoro, and Ramon Andrade De Mello**

**Abstract** The thymic epithelial tumors represent a heterogeneous group of thoracic cancers that originate in the thymus and are in the anterior mediastinum (de Jong WK, Blaauwgeers JL, Schaapveld M et al. *Eur J Cancer* 44:123–130, 2008). They are classified according to the World Health Organization (WHO) in Thymoma and Thymic Carcinoma (Marx A, Chan JK, Coindre JM et al. *J Thorac Oncol* 10:1383–1395, 2015). Thymomas may spread locally, but thymic carcinomas are much more aggressive (Proceedings of the First International Conference on Thymic Malignancies. August 20–21, 2009. Bethesda, Maryland, USA. *J Thorac Oncol* 2010;5:S259–S370, 2009).

**Keywords** Oncology · Chemotherapy · Thoracic oncology

### 12.1 Introduction

The thymic epithelial tumors represent a heterogeneous group of thoracic cancers that originate in the thymus and are in the anterior mediastinum [1]. They are classified according to the World Health Organization (WHO) in Thymoma and Thymic

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Carcinoma [2]. Thymomas may spread locally, but thymic carcinomas are much more aggressive. [3]

It is important to differentiate between thymic cancer and other conditions such as lung metastases, lymphoma (25% of cases), goiter and germ cell tumor (20% of cases) [1, 4]. About 50% of primary cancers in the anterior mediastinum are thymomas [5].

## 12.2 Incidence and Epidemiology

The thymic epithelial tumors present an annual incidence varying from 1.3 to 3.2 per million, with a 5-year survival rate for thymoma and thymic carcinoma of 90% and 55%, respectively [1, 6, 7]. Most patients with thymic neoplasm are between 40 and 60 years of age, with a similar incidence between sexes [8].

Thymomas predominate in adults (rare in children) whereas thymic carcinomas can be found in adolescents [9, 10]. The predominant histologies in thymic carcinoma are squamous cell carcinoma and undifferentiated carcinoma, therefore, they must always be differentiated from metastatic lung carcinoma [11].

There is no known risk factor or etiology, but the relation between thymoma and paraneoplastic syndromes such as myasthenia gravis (MG) is well established. Thymic carcinoma does not have the same relation and it is still unclear whether they both share a cell of common origin [12].

## 12.3 Clinical Manifestation and Diagnosis

### 12.3.1 *Clinical Manifestations*

Some patients are asymptomatic. Clinical presentation in thymomas and thymic carcinomas can be related to the size of the tumor and its effect on adjacent organs, such as cough, dyspnea, chest pain and superior vena cava syndrome. In thymic carcinomas, a more aggressive disease, they may present with lymph node involvement and extrathoracic metastases at diagnosis, as well as pleural and pericardial effusion [7, 13].

Paraneoplastic syndromes are common in thymomas and they can anticipate presentation, occur simultaneously or after treatment (with or without evidence of tumor recurrence). Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases, mainly in types AB, B1 and B2, and frequently associated with anti-acetylcholine antibody. Suggestive symptoms are asthenia, dyspnea, hoarseness, diplopia and ptosis [14–16]. Other immune manifestations include pure red cell aplasia (5%) and hypogammaglobulinemia (Good's Syndrome: 5%). Thymectomy may lead to remission of

MG and pure red cell aplasia [17]. In thymic carcinoma, paraneoplastic syndromes are infrequent [18].

If a thymic epithelial tumor is suspected, a complete physical examination, including neurological examination, should be performed. Immunological evaluation, including blood count, reticulocytes, protein electrophoresis, as well as anti-acetylcholine antibodies and anti-nuclear antibodies should be requested. The presence of autoimmune disorders can affect the course of the disease, interfering with surgery, chemotherapy and radiotherapy [19].

### **12.3.2 Diagnosis**

The standard imaging for the diagnosis of thymic tumors is computed tomography (CT) of the chest with contrast, it allows us to evaluate the mediastinum and pleura [19]. The need for pre-treatment biopsy depends on the resectability of the tumor, when required, the standard is CT- or ultrasound-guided percutaneous needle biopsy. [20–22].

The presence of mass localized in the anterior mediastinum associated with some of the autoimmune diseases mentioned above, closes the presumptive diagnosis of thymoma. Serum levels of lactate dehydrogenase (DHL),  $\beta$ -human chorionic gonadotropin (B-HCG), alphafetoprotein and thyroid hormone should be measured for differential diagnosis with lymphoma, germ cell tumors and goiter [19, 23].

The 18-Fluorodeoxyglucose positron emission tomography scan (PET-CT) is generally not recommended for the evaluation of thymic masses, and may be more useful in thymic carcinomas [24].

## **12.4 Anatomy and Pathology**

The thymus is a lymphatic organ that acts on the maturation of the T lymphocytes. It is an irregular and lobed organ at maturity, slowly involutes in the adult phase, being replaced by adipose tissue. Ectopic thymic tissue can be found throughout the mediastinum and neck, and may be the explanation for thymomas outside the anterior mediastinum [12, 25].

The differentiation between thymoma and lymphoma in small biopsies can be difficult. The WHO classification was designed for surgical resection specimens; however, it may be used in small biopsies, anticipating possible discrepancies between them due to tumor heterogeneity and low sampling [26]. When presenting more than one histological pattern all should be listed and quantified, a component of thymic carcinoma should be listed first when present [19].

The WHO classification system for thymic neoplasms is the most widely used (Table 12.1) [27]. Suster and Moran [28] proposed a simpler classification that divides thymic tumors into 3 categories: Well differentiated (Types A, AB, B1 and B2), moderately differentiated (Type B3) and poorly differentiated (Type C).

**Table 12.1** WHO Histologic Classification [27]

Type	Description
A	A tumor composed of a population of neoplastic thymic epithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes.
AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes.
B1	A tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.
B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular spaces are common and sometimes very prominent. A perivascular arrangement of tumor cells resulting in a palisading effect may be seen.
B3	A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a mild component of lymphocytes, resulting in a sheetlike growth of the neoplastic epithelial cells.
C	A thymic tumor (thymic carcinoma) exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells.

Thymic carcinomas are histologically classified as low or high grade. Low-grade carcinomas include squamous cell carcinomas, mucoepidermoid, and basaloid, generally have a more favorable presentation with a median survival of 25.4 months. High-grade carcinomas include lymphoepitheliomalike, undifferentiated, sarcomatoid, and clear cell carcinomas, which present a worse prognosis with a median survival of 11.3 months [13, 29].

Immunohistochemical markers may be useful, including cytokeratins, p63 expression and deoxynucleotidyl transferase in immature T cells (Absent in type A). In thymic carcinomas immunohistochemistry may presents anti CD117 (KIT) and anti CD5, positive in approximately 80% of carcinomas with thymic origin [30].

Overexpression of EGFR is found in more than two thirds of patients, mostly in subtypes B2 and B3. Overexpression of c-kit is common in thymic carcinomas although its mutation is less frequent. [31, 32]

## 12.5 Staging and Risk Assessment

The most used staging for thymic tumors is Masaoka-Koga (Table 12.2) and is related to overall survival. It is a system of surgical pathology that can only be evaluated after surgical resection [33, 34].

The Tumor-Node-Metastasis staging (TNM) for thymic malignancies was based on an international retrospective database with more than 10,000 cases (Table 12.3)



**Table 12.2** Masaoka Staging System [33]

Stage	Description
I	Macroscopically completely encapsulated and microscopically no capsular invasion
IIA	Microscopic invasion into capsule
IIB	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
III	Macroscopic invasion into neighboring organ, i.e., pericardium, great vessels, or lung
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

**Table 12.3** TNM Classification [35]

<b>T-primary tumor</b>			
T0	No evidence of primary tumor		
T1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura		
A	Tumor with no mediastinal pleura involvement		
B	Tumor with direct invasion of mediastinal pleura		
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)		
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins		
T4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus		
<b>N-regional lymph nodes</b>			
N0	No regional lymph node metastasis		
N1	Metastasis in anterior (perithymic) lymph nodes		
N2	Metastasis in deep intrathoracic or cervical lymph nodes		
<b>M - distant metastasis</b>			
M0	No pleural, pericardial, or distant metastasis		
M1	Pleural, pericardial, or distant metastasis		
A	Separate pleural or pericardial nodule(s)		
B	Pulmonary intraparenchymal nodule or distant organ metastasis		
Stage grouping			
Stage	T	N	M
I	T1a,b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVA	Any T	N0,1	M1a
IVB	Any T	N2	M0,M1a
IVB	Any T	Any N	M1b

and was incorporated into the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system. It has the advantage of being suitable for both thymoma and thymic carcinoma and may be useful in evaluating resectability because the level of T1-T3 invasion refers to structures susceptible to surgical resection while the level of T4 invasion includes non-resectable structures [35].

The main prognostic factor is the complete surgical resection surpassing the tumor stage and the histology [34, 36]. Most patients, up to 50–60% of cases depending on the stage, do not die of tumor progression [37]. One of the causes of death in patients with thymoma are autoimmune disorders, occurring in up to 25% of cases, especially in the early stages [19].

## 12.6 Surgical Treatment

Total thymectomy, including removal of the tumor, residual thymic gland and perithymic fat, is the procedure of choice for resectable thymic tumors in patients who can tolerate surgery, achieving high survival rates at 10 years for thymomas, depending on the integrity of the resection, as in stages I and II with rates of 90 and 70%, respectively [10, 34]. For tumors that invade other structures it is necessary to remove all these structures in block [38].

Removal of anterior mediastinal and anterior cervical lymph nodes is routinely recommended. Sampling of other intrathoracic lymph nodes is suggested in stages III/IV. For thymic carcinomas, systematic lymphadenectomy with a broad lymph node approach is strongly recommended because of the high rates of lymphatic dissemination compared to thymomas (20% × 3%) [39, 40].

For patients with tumor recurrence, surgical resection may result in prolonged survival for selected patients with localized disease [41].

## 12.7 Radiotherapy

Adjuvant radiotherapy is not recommended for fully resected Stage I thymomas and the lymph nodes should not be irradiated routinely because of the low risk of compromising them [33, 42, 43]. For stage II patients completely resected with capsular invasion or aggressive histology (B2/B3), adjuvant radiotherapy may be considered, whereas stage III, due to the high risk of local recurrence, is recommended with a prolongation in recurrence free survival and overall survival [42, 44, 45]. For patients with unresectable disease the dose of 60–70 Gy is recommended [46].

In adjuvant radiotherapy, the recommended dose is 45–50 Gy for patients with free margins, 54 Gy for patients with microscopically positive margins and 60 Gy or more for patients with macroscopic residual disease. Adjuvant radiotherapy should be started ideally within 3 months after surgery [46].

For thymic carcinomas the radiotherapy is recommended the similarity of the thymoma, considering the greater rate of recurrence of the same, being optional in stage I [9, 47].

## 12.8 Chemotherapy

### 12.8.1 Induction Chemotherapy

For the locally advanced thymic tumors, which were considered unresectable in the imaging studies, a biopsy should be performed followed by induction chemotherapy. The most studied regimen is CAP (Cisplatin 50 mg/m<sup>2</sup>, Doxorubicin 50 mg/m<sup>2</sup> and Cyclophosphamide 500 mg/m<sup>2</sup>) every 3 weeks for about two to four cycles before reassessment with overall response rate of 69.6%. [48–50].

Chemoradiotherapy associated with Cisplatin and Etoposide can be performed for thymic carcinomas [51, 52].

### 12.8.2 Chemoradiotherapy

When surgery cannot be performed, either because of poor performance or due to technical difficulties, one option is to offer definitive radiation therapy after chemotherapy or to consider chemoradiotherapy with Cisplatin and Etoposide (60–66 Gy) [19, 50].

### 12.8.3 Adjuvant Chemotherapy

Adjuvant chemotherapy is not recommended for thymomas with complete resection or with microscopic surgical margins [36, 53].

In thymic carcinomas, adjuvant chemotherapy may be considered after incomplete resection, especially when induction chemotherapy has not been offered, due to the high rates of relapse [19].

### 12.8.4 Palliative Chemotherapy

For patients with unresectable/metastatic disease, systemic treatment should be considered to control the symptoms [20]. The most commonly used regimen for thymomas is CAP [54]. Other less aggressive options are Carbo-Px (Carboplatin AUC 5 plus Paclitaxel 200 mg/m<sup>2</sup>) every 3 weeks or PE/VIP (Cisplatin and Etoposide – with or without Ifosfamide), also used as second line therapy [55–57]. As sequential therapies, we have options like Pemetrexed and the combination of

Gemcitabine plus Capecitabine [58, 59]. Re-exposure to a previous regimen should be considered when a good response was initially achieved associated with a long disease-free period [60].

In patients with thymoma and Octreoscan positive, not candidates for chemotherapy, Octreotide (associated or not with Prednisone) may be used [61].

Thymic Carcinoma does not respond well to chemotherapy. The highest response rate in clinical trials is with the Carbo-Px [55]. The ADOC regimen (Cisplatin 50 mg/m<sup>2</sup>, Doxorubicin 40 mg/m<sup>2</sup>, Vincristine 0.6 mg/m<sup>2</sup> and Cyclophosphamide 700 mg/m<sup>2</sup>) is also effective, but it is more toxic than Carbo-Px [62]. Second-line chemotherapy has been poorly studied and is performed as in the thymoma.

## 12.9 Molecularly Targeted Therapy

The molecular characterization of thymic epithelial tumors has identified feasible targets for targeted therapy as molecular changes in KIT, vascular endothelial growth factor (VEGFRs) and mammalian target of rapamycin (mTOR) receptors [63].

Patients with thymic carcinoma may have overexpression of the KIT gene in up to 80% of cases; however, only 10% have the c-kit mutation and in these cases Sorafenib, Sunitinib or Imatinib may be useful as a therapeutic option for refractory tumors (Off-Label) [64, 65]. For patients without c-Kit mutation, Imatinib should not be used. Patients with thymoma do not have a c-kit mutation [66].

Sunitinib may be an off-label option for patients with thymic carcinoma without the c-Kit mutation based on a phase II study that showed response and disease control rate [64]. There is no evidence regarding the use of other anti-angiogenic drugs such as Bevacizumab [19].

Everolimus was also evaluated in a phase II study showing a response rate of 22%, therefore, it can be considered as an off-label option for refractory thymic tumors [67].

## 12.10 Follow-Up

Although there are no clinical trials that show benefit, monitoring with chest images is recommended [20, 33].

A chest CT scan should be ordered 3–4 months after surgery [19].

After treatment for resectable stage I/II thymomas, computed tomography of the chest should be performed annually within the first 5 years and every 2 years thereafter [19]. For stage III/IV thymomas or resected with compromised margins, computed tomography of the chest should be performed every 6 months for the first 2 years and annually thereafter [19, 20].

For resected thymic carcinoma, computed tomography of the chest is recommended every 6 months for the first 2 years and annually thereafter [19, 20].

Follow-up should be maintained for 10–15 years because of the risk of late recurrence, especially in thymomas [68].

Patients with thymoma are at increased risk of developing a second neoplasm such as non-Hodgkin's lymphoma, gastrointestinal cancer, and soft tissue sarcoma [69].

### Questions

1. M. S., 32 years old, female, performed Chest Radiography, which showed mediastinal enlargement, due to cough. During the investigation, he performed a thorax CT that showed mass in the anterior mediastinum without invasion of adjacent structures. She has no history of smoking or other comorbidities. Which the initial conduct?

- A. Biopsy
- B. Follow-up
- C. PET-CT
- D. **Surgery**

**J:** Total thymectomy, including removal of the tumor, residual thymic gland and perithymic fat, is the procedure of choice for resectable thymic tumors in patients who can tolerate surgery, achieving high survival rates at 10 years for thymomas, depending on the integrity of the resection, as in stages I and II with rates of 90 and 70%, respectively.

2. Still on the above case, a thymectomy was performed whose anatomopathological showed a 4 cm encapsulated thymoma without capsular invasion, type A (WHO classification).

What is the stage of this thymoma?

- A. **Masaoka I**
- B. Masaoka II
- C. Masaoka III
- D. Masaoka IV

**J:** The most used staging for thymic tumors is Masaoka-Koga and is related to overall survival. It is a system of surgical pathology that can only be evaluated after surgical resection.

The Masaoka staging:

Stage	Description
I	Macroscopically completely encapsulated and microscopically no capsular invasion
IIA	Microscopic invasion into capsule
IIB	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
III	Macroscopic invasion into neighboring organ, i.e., pericardium, great vessels, or lung
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

3. According to the surgical staging above, what would be the most appropriate therapy?

- A. **Clinical Surveillance**
- B. Adjuvant radiotherapy
- C. Adjuvant chemotherapy
- D. Radiation therapy followed by chemotherapy

**J:** Adjuvant radiotherapy is not recommended for fully resected Stage I thymomas and the lymph nodes should not be irradiated routinely because of the low risk of compromising them. Adjuvant chemotherapy is not recommended for thymomas with complete resection or with microscopic surgical margins.

4. F. S., 52 years old, male, was admitted to the emergency room due to intense asthenia, palpebral ptosis and diplopia. Laboratory tests were performed to show the presence of the anti-acetylcholine antibody. An anterior mediastinal mass was visualized on chest CT.

What is the probable diagnosis?

- A. Germ cell tumor
- B. **Thymoma**
- C. Thymic Carcinoma
- D. Goiter

**J:** The presence of mass localized in the anterior mediastinum associated with some of the autoimmune diseases mentioned above, closes the presumptive diagnosis of thymoma. Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases, mainly in types AB, B1 and B2, and frequently associated with anti-acetylcholine antibody.

5. What treatment could bring remission of the paraneoplastic syndrome mentioned above?

- A. Chemotherapy
- B. Radiotherapy
- C. **Thymectomy**
- D. Clinical treatment only

**J:** Paraneoplastic syndromes are common in thymomas and they can anticipate presentation, occur simultaneously or after treatment (with or without evidence of tumor recurrence). Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases. Other immune manifestations include pure red cell aplasia (5%) and hypogammaglobulinemia (Good's Syndrome: 5%). Thymectomy may lead to remission of MG and pure red cell aplasia.

6. Which tests should be performed in the differential diagnosis of mediastinal mass?
- lactate dehydrogenase
  - $\beta$ -human chorionic gonadotropin and alphafetoprotein
  - thyroid hormone
  - All above**

**J:** Serum levels of lactate dehydrogenase (DHL),  $\beta$ -human chorionic gonadotropin (B-HCG), alphafetoprotein and thyroid hormone should be measured for differential diagnosis with lymphoma, germ cell tumors and goiter.

7. What are the main paraneoplastic syndromes associated with thymoma?
- Myasthenia gravis
  - Pure red cell aplasia
  - Good's Syndrome
  - All above**

**J:** Up to one third of patients presents with autoimmune disorders, most frequently with myasthenia gravis (MG) in up to 30–50% of cases. Other immune manifestations include pure red cell aplasia (5%) and hypogammaglobulinemia (Good's Syndrome: 5%).

8. L. L., 44 years old, female, underwent thymectomy, whose pathological anatomy revealed thymic carcinoma with macroscopic invasion of neighboring structures and incomplete resection.

What's the next conduct?

- Clinical Surveillance
- Radiotherapy with 54 Gy
- Radiotherapy with 60 Gy**
- Chemotherapy

**J:** Adjuvant radiotherapy is recommended for stage II patients completely resected with capsular invasion or aggressive histology (B2/B3), whereas stage III, due to the high risk of local recurrence, is recommended with a prolongation in recurrence free survival and overall survival. In adjuvant radiotherapy, the recommended dose is 45–50 Gy for patients with free margins, 54 Gy for patients with microscopically positive margins and 60 Gy or more for patients with macroscopic residual disease. Adjuvant radiotherapy should be started ideally within 3 months after surgery.

9. Which histology of thymic carcinoma is associated with an unfavorable outcome?
- Squamous cell carcinoma
  - Clear Cell Carcinoma**
  - Mucoepidermoid Carcinoma
  - Basaloid Carcinoma

**J:** Thymic carcinomas are histologically classified as low or high grade. Low-grade carcinomas include squamous cell carcinomas, mucoepidermoid, and basaloid,

generally have a more favorable presentation with a median survival of 25.4 months. High-grade carcinomas include lymphoepitheliomalike, small, undifferentiated, sarcomatoid, and clear cell carcinomas, which present a worse prognosis with a median survival of 11.3 months.

10. What is the main prognostic factor in thymic epithelial tumors?

- A. **Complete resection**
- B. Age
- C. Sex
- D. Presence of paraneoplastic syndrome

**J:** Total thymectomy, including removal of the tumor, residual thymic gland and perithymic fat, is the procedure of choice for resectable thymic tumors in patients who can tolerate surgery, achieving high survival rates at 10 years for thymomas, depending on the integrity of the resection, as in stages I and II with rates of 90 and 70%, respectively. For tumors that invade other structures it is necessary to remove all these structures in block.

11. Paraneoplastic syndromes manifest in what period of the disease?

- A. Before diagnosis
- B. During illness
- C. After treatment
- D. **All above**

**J:** Paraneoplastic syndromes are common in thymomas and they can anticipate presentation, occur simultaneously or after treatment (with or without evidence of tumor recurrence).

12. For locally advanced thymic tumors what is the best therapeutic option?

- A. Surgery
- B. Radiation Therapy + Chemotherapy
- C. **Induction chemotherapy**
- D. Palliative chemotherapy

**J:** For the locally advanced thymic tumors, which were considered unresectable in the imaging studies, a biopsy should be performed followed by induction chemotherapy. The objective of induction chemotherapy is to achieve complete tumor resection, which improves overall survival.

13. What is the most studied chemotherapy regimen for locally advanced thymoma?

- A. **CAP**
- B. Carboplatin Plus Paclitaxel
- C. Cisplatin plus Etoposide
- D. Ifosfamide

**J:** The most studied regimen is CAP (Cisplatin 50 mg/m<sup>2</sup>, Doxorubicin 50 mg/m<sup>2</sup> and Cyclophosphamide 500 mg/m<sup>2</sup>) every 3 weeks for about two to four cycles before reassessment with overall response rate of 69.6%.



14. What is the first choice in the palliative treatment of thymic carcinoma?

- A. CAP
- B. **Carboplatin Plus Paclitaxel**
- C. Cisplatin plus Etoposide
- D. Ifosfamide

**J:** Thymic Carcinoma does not respond well to chemotherapy. The highest response rate in clinical trials is with the Carboplatin AUC5 plus Paclitaxel 200 mg/m<sup>2</sup> every 3 weeks with objective response rate of 21,7%. Progression-free survival (PFS) was 5 months and Median survival time was 20.0 months.

15. Which of the following schemes can be used as a second line?

- A. CAP
- B. Carboplatin Plus Paclitaxel
- C. Gemcitabine plus Capecitabine
- D. **All above**

**J:** The most commonly used regimen for thymomas is CAP. Other less aggressive options are Carbo-Px (Carboplatin AUC 5 plus Paclitaxel 200 mg/m<sup>2</sup>) every 3 weeks or PE/VIP (Cisplatin and Etoposide – with or without Ifosfamide), also used as second line therapy. As sequential therapies, we have options like Pemetrexed and the combination of Gemcitabine plus Capecitabine. Re-exposure to a previous regimen should be considered when a good response was initially achieved associated with a long disease-free period

### Clinical Case

M.C.T., 40 years old, born in Pernambuco, begins follow-up with clinical neurology in 2010 complaining of intense asthenia associated with diplopia. During the investigation carried out research of antibodies with positivity of the anti-acetylcholine antibody.

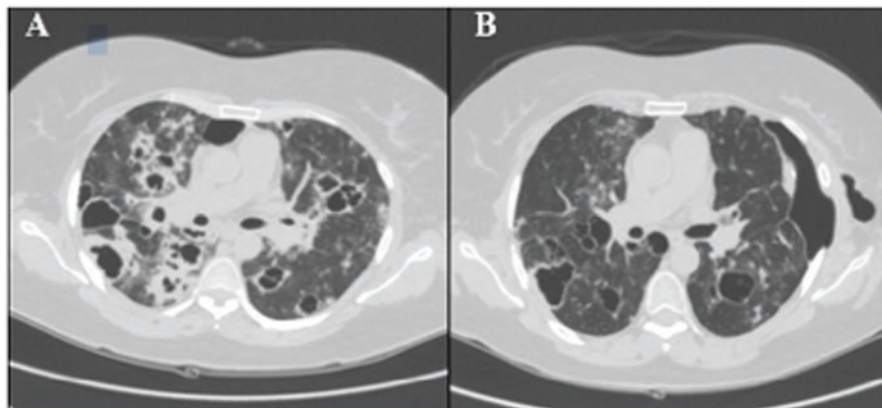
With the diagnosis of myasthenia gravis, a chest CT scan (Fig. 12.1) revealed a mass of finely heterogeneous attenuation in the thymus topography, measuring 3.0 × 1.5 cm, which may correspond to thymic neoplasia.

She was no history of comorbidities. It was opted for thymectomy with the diagnosis of Thymoma B3 by WHO classification and Masaoka I staging.

During follow-up with neurology she presented some exacerbations of myasthenia gravis, the last one being in 2015, maintaining the use of Pyridostigmine and Prednisone.

In 2015, it was visualized in chest CT two pleural nodules, one in right apex measuring 7.0 × 5.1 cm and other pleurodiaphragmatic measuring 3.7 × 1.3 cm. Biopsy confirmed recurrence of Thymoma B3.

It was discussed case with the Thoracic Surgery and they opted for induction chemotherapy with CAP. After the first cycle patient presented respiratory symptoms associated with neutropenia grade 4 and needed hospitalization for administration of antibiotics. After the third cycle, although with the administration of granulocyte colony stimulating factor, the patient is admitted to an intensive care unit due to pneumonia and grade 4 neutropenia/thrombocytopenia, requiring orotracheal intubation.



**Fig. 12.1** (a) Chest CT performed on 07/2017 showing bilateral cavitary lesions with soft tissue density content. (b) Chest CT performed on 09/2017, after antibiotic therapy and immunoglobulin infusion, showing reduction of cavitations. (Source: Provided by the Department of Clinical and Experimental Oncology of UNIFESP)

It was performed chest CT after the fourth cycle with partial response of the lesions, measuring  $3.5 \times 3.1$  cm located at the apex of the lung and  $1.6 \times 0.8$  cm at pleurodiaphragmatic.

After 40 days of the end of chemotherapy, the patient performs thoracotomy with complete resection of pleural lesions (Thymoma B3) and mediastinal fat (Absence of neoplasia)

The patient remained in follow-up for 2 years, during which time she had several upper respiratory infections, pulmonary tuberculosis and hospitalization due to widespread herpes zoster.

In 2017 presented pulmonary infection with a need for hospital admission, on CT of thorax visualized bilateral excavated nodules and ground glass opacities associated with right hilar lymph node measuring 1.3 cm. Biopsy performed with diagnosis of pneumocystosis.

In laboratory tests and immunoglobulin dosages detected IgM  $<5.0$  UI/ml, IgG  $<30.0$  UI/ml and IgA 43 UI/ml. Lymphocytes: CD3 2046 células/mm<sup>3</sup>; CD4 1006 células/mm<sup>3</sup>; CD8 1246 células/mm<sup>3</sup>; CD19 0 células/mm<sup>3</sup> and NK 111 células/mm<sup>3</sup>. After confirmed the diagnosis of Good's Syndrome was initiated follow-up with immunology and realized monthly Immunoglobulin infusions.

After the fourth application and beginning of specific treatment, there was clinical and laboratory improvement. In the last staging, the patient was no evidence of disease, with improvement of the cavitated lesions.

This case illustrates the potential of the thymoma to manifest paraneoplastic syndromes. Up to one third of patients can present with autoimmune disorders, most frequently myasthenia gravis (MG) in up to 30–50% of cases. The hypogammaglobulinemia (Good's Syndrome) can be present in up to 5% of cases. (Fig. 12.1).

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# Chapter 13

## Breast Cancer



Inês Monteiro, Teresa Alvarez, Jean-Yves Meuwly, and Khalil Zaman

**Abstract** Breast cancer is not a single disease. It is highly heterogeneous in its molecular biology and natural evolution, impacting treatment response and prognosis. It is one of the most prevalent cancers worldwide with high impact on individual, social and economic levels. Nowadays, breast cancer treatment demands a multidisciplinary approach and the involvement of informed patients. Personalized breast cancer care should mean both considering the prognostic and predictive biomarkers of a single tumor and considering an individual patient's preferences.

**Keywords** Breast cancer · Biomarkers · Targeted therapy

### Abbreviations

AI	Aromatase inhibitor
BC	breast cancer
CDK4/6	cyclin-dependent kinases 4/6
cD1	cyclin D1
CT	computed tomography
ER	estrogen receptor
ET	endocrine therapy
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
LN	lymph node

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mAb	monoclonal antibody
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
NST	no special type
OFS	ovarian function suppression
OS	overall survival
PARP	poly-adenosine diphosphate-ribose polymerase inhibitor
pCR	pathological complete response
PET-CT	positron emission computed tomography
PFS	progression-free survival
PR	progesterone receptor
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
TILs	tumor-infiltrating lymphocytes
TNM	tumor node metastasis

### 13.1 Introduction

Breast cancer (BC) is a highly prevalent type of cancer, with high personal, social and economic impact. The knowledge regarding physiopathology, prevention and treatment has frankly evolved in the past few years. Nowadays, BC management should involve a multidisciplinary team. Unfortunately, BC management may vary substantially depending on patient's location on the globe and the availability of care.

### 13.2 Epidemiology and Risk Factors

BC is the most frequent cancer in women and the second most common in the world, estimated by the World Health Organization at 12% of new cancers in 2012. It is the first cause of cancer death in women in most countries and the second behind lung cancer in some others. Globally, it is the 5th cause of cancer death [1].

The age-standardized rates of incidence and mortality of BC per 100,000 women in 2012 distributed as follows (incidence/mortality): Africa 36/17, Asia 29/10, Europe 70/16, North America 92/15, Oceania 79/16 and South America 52/14. African countries presented the lowest 5-year survival rates, probably due to late stage at diagnosis and limited accessibility to treatment [1, 2]. BC prevalence is increasing worldwide due to better screening, ageing of the population and improved outcomes [3].

Female gender, aging and family history are some of the most important risk factors for BC [4]. Mammographic breast density is also an independent risk factor for



the development of BC [5]. Reproductive factors such as early menarche (<12 years), late menopause (>55 years), advanced age at first pregnancy and low parity, increase BC risk [2]. Exogenous estrogens are also risk factors. Hormone-replacement therapy, mainly in the presence of progestin, increases the incidence of BC in a time-dependent manner [6, 7]. Oral contraceptives may increase the risk of BC but there is no significant excess risk 10 years after discontinuation [8]. Smoking, alcohol consumption and exposition to irradiation increase the risk of BC. Obesity in post-menopausal women increases BC risk, contrarily to physical activity, which is a protective factor [2, 4]. Some germinal gene mutations predispose to BC (*ATM*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, *STK11*, *TP53*) [9].

Male BC is rare ( $\approx 1\%$  of cases). Major risk factors include genetic predisposition (as *BRCA* mutation), hormonal imbalances and radiation exposure [10].

### 13.3 Breast Cancer Screening

BC secondary prevention relies mostly on mammography screening programs. Despite some controversies about the real benefit of BC screening, a 15–20% decrease of the relative BC mortality risk is described [11, 12]. Disadvantages of screening are discomfort, stress, investigations related to false-positive results and overdiagnosis. Before screening, careful discussion about benefits and risks is imperative. There is no worldwide consensus about the age range of the screened population and the frequency of the mammography. However, all the screening programs propose at least one mammography yearly to 3-yearly for women between 50 and 70 years [13, 14].

In case of first degree family history, the first imaging should be considered 10 years before the age of the earliest diagnosis. For women with high risk genetic predisposition annual magnetic resonance imaging (MRI) concomitantly or alternating every 6 months with mammography, is recommended since the age of 20–30 depending on the concerned gene [13, 14].

### 13.4 Diagnosis and Staging

BC diagnosis is based on clinical evaluation in combination with imaging exams and confirmed by pathological analysis (Table 13.1).

Medical history should include family history of breast, ovarian and other cancers, age at menarche, age at first delivery, number of pregnancies and births, history of breast biopsies and interventions, menopausal status and use of hormone replacement therapy or hormonal contraception. For women with child-bearing potential, the desire of future pregnancies should be addressed as soon as possible to enable referral to fertility specialists and counseling on fertility preserving options before the start of systemic treatments [15].

**Table 13.1** Diagnostic workup for breast cancer

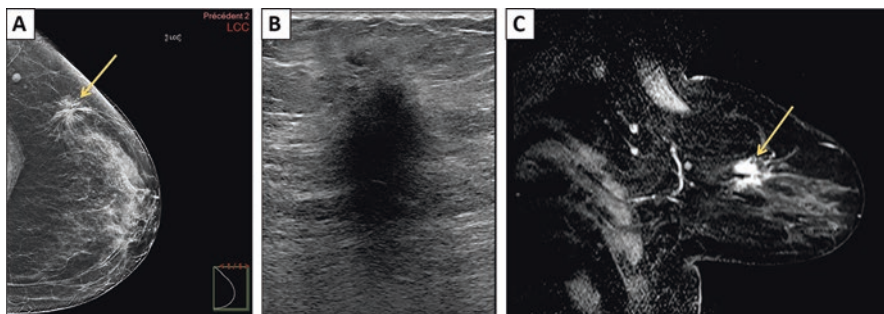
Anamnesis (emphasis on gynecological and obstetric history and oncological family history)
Patient's desires regarding fertility preservation
Breast and locoregional lymph nodes inspection and palpation
Mammography and ultrasound of the breasts (MRI for selected cases)
Axillary ultrasound
Preoperative complete pathological assessment of the breast lesion (core biopsy): histological subtype, grade and ER, PR, HER2 and Ki67 status
Ultrasound-guided LNB if suspicious LN
Distant staging with thoracic, abdominal or full-body CT or PET-CT, liver ultrasound, chest X-ray and/or bone scan should only be considered for patients with symptoms/signs of distant metastasis or loco-regionally advanced disease
Full blood count, renal and hepatic function tests, calcium and phosphatase alkaline levels
Echocardiography (when considering treatment with anthracyclines or anti-HER2 treatments)
Establishing the clinical prognostic stage
Discussion of the case in a multidisciplinary breast cancer tumor board

*CT* computed tomography, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *LNB* lymph-node biopsy, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *PR* progesterone receptor

Both breasts should be inspected and palpated with the patient sitting or standing and lying supine. Locoregional lymph nodes should also be palpated. Most frequent signs of BC are breast lumps (60% of patients), pain, breast asymmetry, skin or nipple retraction, nipple inversion, nipple discharge, skin rash and ulceration. Inflammatory carcinoma characteristically causes erythema and edema of at least one third of the breast [16], posing a differential diagnosis with inflammatory conditions. Paget's disease of the breast is a pruritic eczema-like rash of the nipple-areola complex accompanying 1–4% of BCs. When present, it is associated with invasive or in situ carcinoma in approximately 90% of patients [16–18].

Imaging exams include bilateral mammography and ultrasound of the breast and regional lymph nodes. MRI is controversial and should be particularly considered in case of genetic predisposition, breast implants, suspicion of multifocality/multicentricity (especially if lobular carcinoma), dense breasts, discrepancy between imaging and clinical assessment or before neoadjuvant treatment [13]. Findings suggestive of cancer in mammography include an irregular mass, stellate or spiculated lesions and microcalcifications. In ultrasound imaging, BC is usually seen as an irregular, hypoechoic lesion [16] (Fig. 13.1).

In developed countries, >90% of BCs present local or regional extension when first diagnosed and asymptomatic distant metastasis are rare. Thus, patients with early disease (until stage IIA) do not benefit from comprehensive radiological staging [13]. For patients with symptoms or laboratory values suggestive of distant metastasis, clinically positive axillary nodes or large tumors (e.g.  $\geq 5$  cm), a computed tomography (CT) scanning of the chest, CT scanning or ultrasound of the abdomen and a bone scan are considered. Positron emission tomography (PET)-CT seems more sensitive, gives information simultaneously on organs and bone, and can be used depending on the availability of the technic [13].



**Fig. 13.1** Imaging findings suggestive of breast cancer. (a) Mammography. Spiculated lesion of the upper quadrant (arrow); (b) Ultrasound. Hypoechoic, poorly delimited lesion; (c) MRI. Spiculated lesion (arrow)

Pathological assessment of the primary lesion is mandatory before initiating therapy. A core biopsy is the most adequate procedure to determine histological type, grade and biomarkers status [19]. In the presence of clinically or radiological suspicious lymph nodes, an ultrasound-guided biopsy should be considered if feasible [13]. In case of distant disease, the biopsy of one metastasis can also be useful, especially in the presence of oligometastases.

The clinical tumor-node-metastasis (cTNM) staging system records the anatomical extent of the disease and is known after clinical and imaging exams [19, 20]. The 8th edition of the clinical prognostic stage groups (0–IV) rely on cTNM and biopsy findings (histological grade and biomarker status) [19]. These stage groups are an attempt to aggregate patients with similar survival outcome.

Before surgery or neoadjuvant treatment, a full blood count, renal and hepatic function tests, calcium and alkaline phosphate levels should be assessed. When considering treatment with anthracyclines or anti-human epidermal growth factor receptor 2 (HER2) treatments, evaluation of cardiac function is recommended [13].

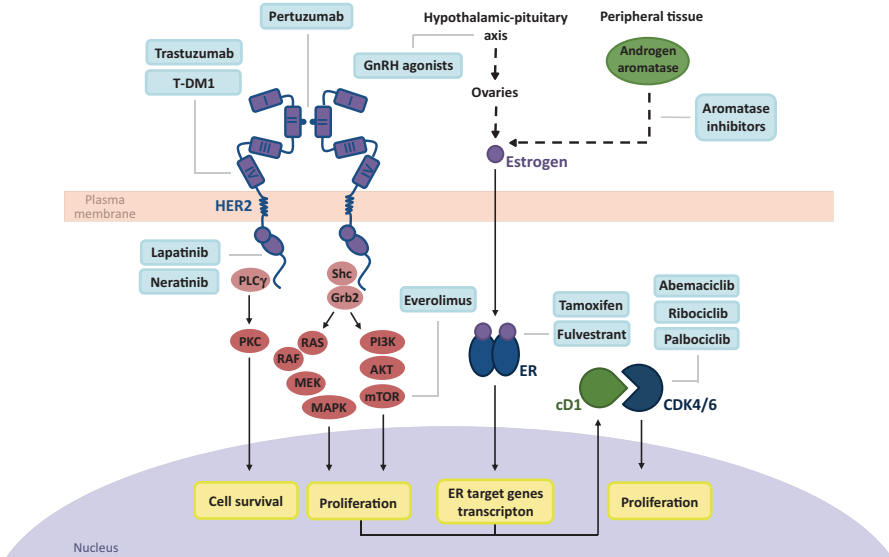
Discussing the treatment strategy in a multidisciplinary BC tumor board improves the quality of care and is recommended.

### 13.5 Molecular Pathways

BC is a very heterogeneous disease. Familiarity with its molecular basis is essential to understand intrinsic subtypes, their morphological counterparts, targeted treatments, treatment-response and novel therapy-options.

Main predictive factors for BC are estrogen receptor (ER), progesterone receptor (PR), HER2, Ki67, BRCA1/2 and PI3K [19] (Fig. 13.2).

Estrogen binding to the ER initiates two pathways: the nuclear (or classical) and the nonnuclear (or alternative) pathway. In the nuclear pathway, ER dimerizes and forms, together with coregulatory proteins, the ER-complex, which interacts with the estrogen response element and modulates gene transcription. The nonnuclear



**Fig. 13.2** Molecular pathways and targeted therapies in breast cancer. Only a HER2 homodimer is represented, however, HER2 can dimerize with other receptors (namely HER1, also called EGFR, HER3 and HER4). Most arrows portray processes that require several steps. For simplicity, only PI3K/AKT/mTOR, RAS/RAF/MEK/MAPK and PLC $\gamma$ /PCK pathways and their main signaling outcomes are shown. Proteins that directly bind phosphotyrosine residues are represented in light pink while subsequently activated proteins are represented in dark pink. There are several groups of drugs (blue rectangles) represented: (i) monoclonal antibodies (targeting the extracellular domain of HER2); (ii) protein kinase inhibitors (binding to HER2’s intracellular portion, mTOR or CDK4/6); (iii) selective estrogen receptor modulators (interacting with ER); (iv) agonists of the GnRH receptor and (v) inhibitors of the enzyme aromatase. This figure is not drawn to scale. *cD1* cyclin D 1, *CDK4/6* cyclin-dependent kinases 4/6, *ER* estrogen receptor, *GnRH* gonadotropin-releasing hormone, *T-DM1* Ado-trastuzumab emtansine

pathway consists of the ER activity in the cytoplasm, where it interacts with multiple signaling pathways (including MAPK and PI3K/AKT pathways). These cross-talks modulate ER activity and can promote resistance to endocrine therapy [21].

The ER and PR have a complex relationship. In BC, they are both regulated by estrogen, their expression is often correlated and their actions converge on pathways that promote tumorigenesis [21].

HER2, a transmembrane tyrosine kinase, belongs to the epidermal growth factor receptor (EGFR) family and is encoded by the *ERBB2* gene. HER2 overexpression occurs mainly due to *ERBB2* gene amplification and, less frequently, mutation. When active, HER2 dimerizes and activates downstream pathways promoting cancer cell survival and proliferation [22]. HER2’s multiple interactions with different pathways and membrane receptors underpin the development of resistance to some treatments.

Some of the most important intracellular pathways in BC are PI3K/AKT, Ras/Raf/MEK/MAPK and PLC- $\gamma$  pathways. The first has an important role in cell survival and the second and third ones mainly mediate cell proliferation. PI3K pathway seems to be a pivotal player in BC and approximately 30% of BCs have mutations

in *PIK3CA* [23]. Once again, these pathways are interconnected and modulate gene expression and treatment-response [21, 24].

The cyclin D1 (cD1)/cyclin-dependent kinases (CDKs) 4/6 pathway is particularly active in ER-positive BC as cD1 is a direct transcriptional target of ER. Upon binding to cD1, CDK4 and CDK6 lead to the expression of genes required for entering the S-phase of the cell cycle, promoting proliferation [21].

## 13.6 Pathology

Pathological assessment is a crucial part of diagnosis and staging of BC. The pathological evaluation of the core biopsy allows a first description of histological type, grading and biomarker status (ER, PR, HER2 and Ki67). After surgery, evaluation of the surgical specimen allows final assessment of tumor size (pT) and description of other prognostic factors such as peritumoral lymphovascular invasion, presence of carcinoma *in situ*, resection margins status and nodal invasion (pN). Histological grade is reevaluated and biomarker status repeated, if needed [19, 25].

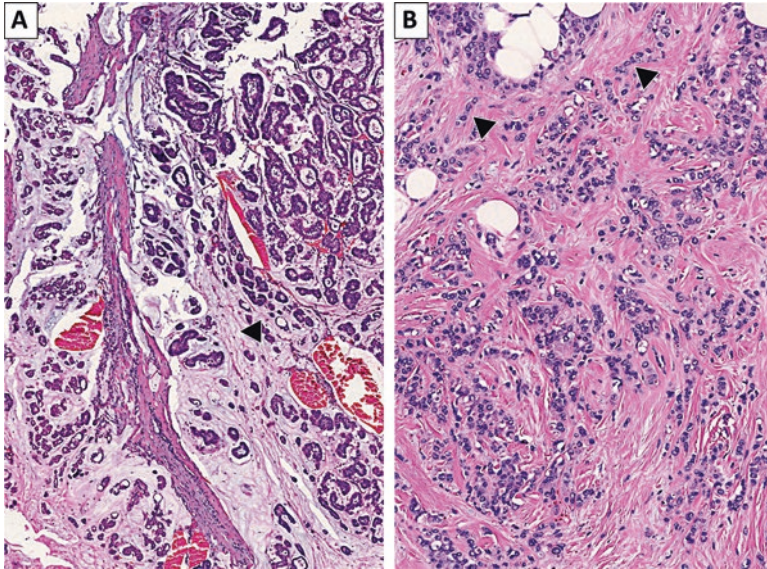
Histological types of breast carcinoma are defined according to the World Health Organization classification (resumed in Table 13.2 and represented in Figs. 13.3 and 13.4) [25]. There are two main types of lesions: invasive and *in situ*.

**Table 13.2** Breast cancer histological subtypes

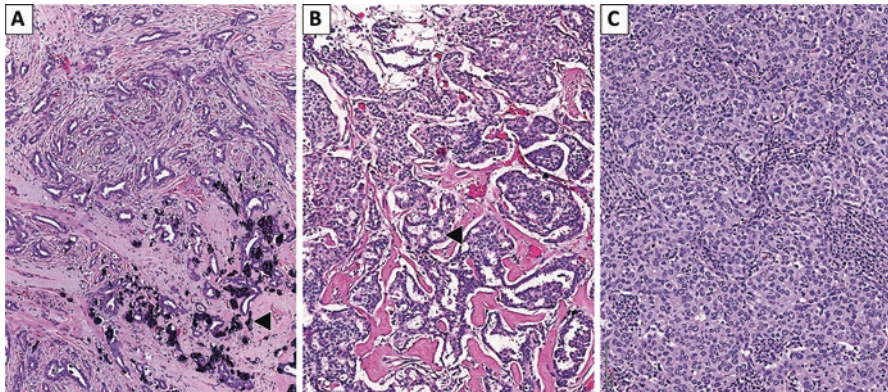
Histological subtype	Frequency
<b>Invasive lesions</b>	
Invasive carcinoma of NST	40–75%
<b>Invasive carcinomas of special type</b>	
Invasive lobular carcinoma	5–15%
Tubular carcinoma	2%
Cribriiform carcinoma	0.3–0.8%
Carcinoma with medullary features	<1%
Metaplastic carcinoma	0.2–5%
Carcinomas with apocrine differentiation	4%
Mucinous carcinoma	2%
Invasive micropapillary carcinoma	0.9–2%
<b>Pre-neoplastic lesions</b>	
Ductal carcinoma <i>in situ</i>	Accompanying 80% of NST carcinomas and accounting for 20–30% of diagnoses of carcinoma from BC screening [16, 25]

*NST* no special type

Based on the “WHO Classification of Tumours of the Breast” [25]



**Fig. 13.3** Breast cancer histological types. (a) Invasive mucinous carcinoma: small, uniform tumor cells floating in lakes of extracellular mucin (arrow head); (b) Invasive lobular carcinoma: non-cohesive tumor cells dispersed or arranged in a single-file linear pattern (arrow heads)



**Fig. 13.4** Invasive breast carcinoma of no special type (NST) and breast cancer grading by Elston and Ellis. (a) Grade 1 NST carcinoma (>75% of the tumor presenting tubular formation, small, uniform cells, low mitotic count). Microcalcifications (arrow head); (b) Grade 2 NST carcinoma (10–75% of tubule formation: arrow head); (c) Grade 3 NST carcinoma (<10% of the tumor presenting tubule formation, marked nuclear pleomorphism)

Invasive breast carcinoma of no special type (NST) (previously known as invasive ductal carcinoma) represents 40–75% of invasive BCs. It comprises a heterogeneous group of tumors with very different prognosis, which fail to exhibit sufficient characteristics to be classified as a specific histological type. The histology is var-

ied: glandular differentiation, solid pattern or disposition of tumor cells in cords, clusters or trabeculae are possible [25].

Among invasive breast carcinomas of special type, lobular carcinoma is the most frequent, representing 5–15% of cases. It has distinctive histological features: non-cohesive cells dispersed or arranged in a single-file linear pattern [25]. This pattern explains its aspect as a poorly delimited lesion in mammography and the difficulty in assessing its size [25, 26]. IHC analysis shows no expression of epithelial cadherin (E-cadherin) in about 85% of lobular carcinomas [25].

Tubular, cribriform, mucinous and adenoid cystic carcinomas have low-grade features and a better prognosis. Carcinomas with medullary features also have a relatively good outcome, attributed to the presence of a prominent lymphoplasmocytic infiltrate. In contrast, micropapillary and metaplastic carcinomas have an unfavorable prognosis. Metaplastic carcinomas present squamous or mesenchymal-looking differentiation, are typically triple-negative and have poorer outcomes [16, 27].

Finally, carcinomas of mixed type have a special pattern in at least 50% of the tumor and 10–49% of NST pattern [25].

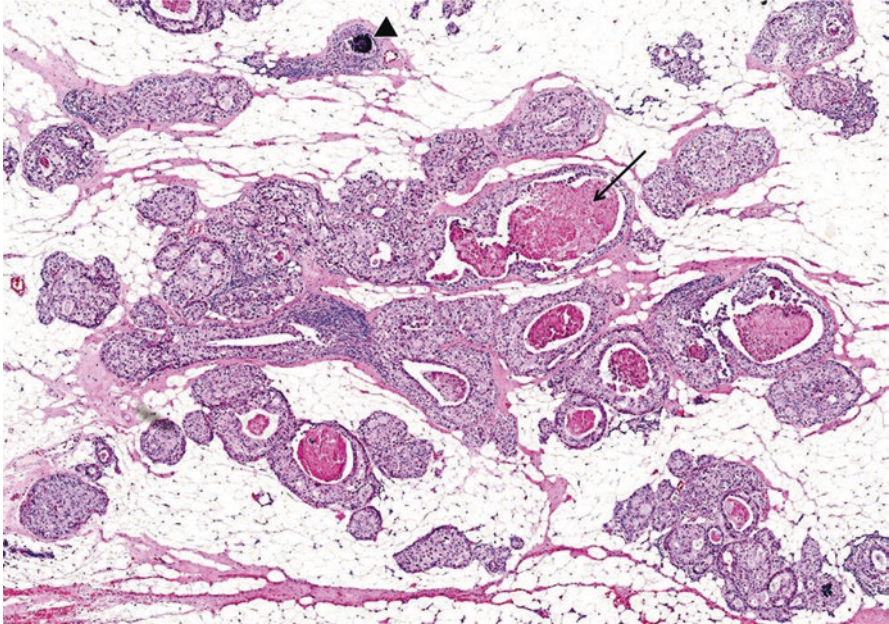
Histological grade (G) in invasive carcinomas is assessed by the Elston and Ellis (or Nottingham) grading system [19] (Fig. 13.4). This grading system is based on three tumor features: tubule formation, nuclear atypia/pleomorphism and mitotic count. Each is evaluated with a score of 1–3. The final sum reflects the grade: 3–5 well differentiated tumor (G1); 6–7 moderately differentiated (G2); 7–9 poorly differentiated (G3) [19].

While histological variants of invasive breast carcinoma are well established, the classification of atypical, non-invasive proliferative intraepithelial lesions, which are now increasingly detected by mammography, is still debated [25]. Different grades of malignancy depend on histological type (ductal or lobular), structure, atypia, necrosis and mitosis. Among non-invasive carcinomas, the two main entities are ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS).

DCIS is a pre-neoplastic lesion (Fig. 13.5). DCIS can be found in association with invasive carcinoma (DCIS is present in up to 80% of NST carcinomas) [19, 25]. The pathology report usually includes nuclear grade (low, intermediate or high grade, assessed following the Van Nuys criteria) [28], hormonal-status (ER/PR), histological pattern, presence of microcalcifications and necrosis and distance to closest margin [16, 19]. Treating DCIS is recommended to prevent the development of invasive carcinoma.

Contrarily, LCIS is considered a risk factor for the development of subsequent invasive cancer in either breast, of either ductal or lobular type. Therefore, it does not usually require treatment [25].

Microscopic evaluation of lymph nodes (LN) defines pathological nodal (pN) status. In the case of suspicious ganglia a biopsy is indicated. If a LN metastasis is confirmed, complementary treatment (e.g. axillary dissection) should be considered. In clinical node-negative disease, a sentinel lymph node (SLN) biopsy should be performed. SLN is the first lymph node to which cancer cells are most likely to spread from a primary tumor. Pathological nodal staging after SLN biopsy (SLNB)



**Fig. 13.5** Ductal carcinoma in situ. Neoplastic cells without evidence of invasion through the basement membrane into the surrounding stroma. Microcalcifications (arrow head) and comedonecrosis (arrow) are present

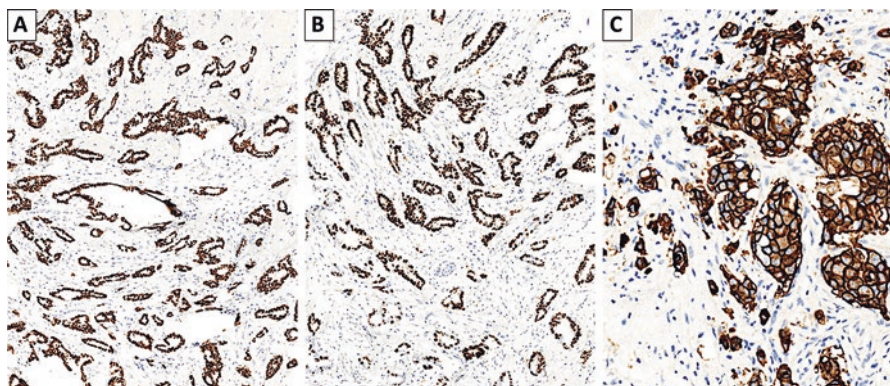
is indicated by adding the “(sn)” suffix (e.g. pN0(sn)). LN metastasis are defined as isolated tumor cells (<0.2 mm; pN0(i+)), micrometastasis (0.2–2 mm; pN1(mi)) and macrometastasis (>2 mm) [19].

Concerning the assessment of predictive factors, ER and PR status is determined by IHC and is usually described as percentage of tumor cells stained. Any staining of  $\geq 1\%$  of tumor cells is considered positive [29] (Fig. 13.6).

*HER2* gene amplification status can be determined directly by *in situ* hybridization (ISH) or, more commonly, by IHC, recurring to ISH in case of ambiguous IHC score. *HER2* status is defined by IHC as negative (score 0: no staining; or 1+: incomplete faint membrane staining within <10% of tumor cells), ambiguous (2+: membrane staining that is incomplete and/or weak/moderate within >10% of tumor cells or complete and intense membrane staining within <10% of tumor cells) or positive (3+: >10% of tumor cells presenting strong complete membrane staining) [30] (Fig. 13.6). ISH is considered positive if the number of *HER2* gene copies is  $\geq 6$  or if the ratio *HER2*/chromosome 17 is  $\geq 2$  [30]. If both the IHC and the ISH evaluations conclude an ambiguous status, using an anti-*HER2* therapy should be discussed with the multidisciplinary board [13].

Proliferation status is assessed by IHC of the Ki67 antigen, most commonly with the MIB1 antibody, and is expressed as percentage of positive cells. So far, no validated cutoff has been defined. More than 30% and less than 15% of tumor cells are





**Fig. 13.6** Breast cancer biomarkers. (a) Immunohistochemistry (IHC) with an anti-ER antibody (atb) (nuclear staining); (b) IHC with an anti-PR atb (nuclear staining); (c) IHC with an anti-HER2 atb (>10% of tumor cells presenting strong complete membrane staining: score 3+)

**Table 13.3** Breast cancer intrinsic subtypes

Intrinsic subtypes	Surrogate intrinsic subtypes	ER	PR	HER2	Ki67 <sup>a</sup>	Grade	Frequency <sup>b</sup>
Luminal A	Luminal A-like	↑	↑	–	↓	1–2	50–60%
Luminal B	Luminal B-like	↓	↓	–	↑	2–3	10–20%
HER2-enriched	HER2-like	↑/↓	↑/↓	+	NA	NA	10–15%
Basal-like	Triple negative	–	–	–	NA	NA	10–20%

ER estrogen receptor, HER2 human epidermal growth factor receptor 2, NA non applicable, PR progesterone receptor

<sup>a</sup>No defined cutoff

<sup>b</sup>Frequencies are based on Ref. [35]

used as references to clearly high and clearly low Ki67 expression [31, 32]. In borderline situations (15–30%) the use of molecular tests might be of use [33].

The acknowledgment of the molecular heterogeneity of BC, led to a reclassification of BC according to its molecular alterations. There are four intrinsic BC subtypes, defined by gene expression profiling [34] (Table 13.3). The four surrogate intrinsic subtypes are based on the original subtypes. They are an attempt to categorize BC and to predict treatment-response in daily practice, relying on accessible methods like immunohistochemistry (for biomarker status) and histological grade [13, 19] (Table 13.3).

Luminal A-like cancers are low-grade, with high expression of endocrine receptors and low proliferation rates. They have small benefit from adjuvant chemotherapy but high benefit from endocrine therapies (ETs). More commonly, they consist of NST or special carcinomas (tubular, cribriform or mucinous) with better prognosis.

Luminal B-like tumors tend to be poorly differentiated, to express less endocrine receptors and to have higher proliferation rates, responding better to adjuvant chemotherapy and poorer to ET.

MammaPrint®, a 70 genes signature, and Oncotype Dx®, a 21 genes signature, have been validated as predictive factors of benefit from adjuvant chemotherapy in endocrine-sensitive BC [19].

HER2-like carcinomas present HER2 overexpression and variable ER/PR expression. The prognosis associated with this BC subtype has significantly changed after the introduction of anti-HER2 therapies.

Triple negative tumors express neither endocrine nor HER2 receptors. As a result, they are challenging to treat and present worse prognosis. The terms basal-like and triple negative are often used interchangeably, however 20% of basal-like tumors are not triple negative [13, 19].

After surgery, residual tumor (R) burden should be classified as no residual tumor (R0), microscopic residual tumor (R1) or macroscopic residual tumor (R2). Generally, R1 is defined as invasive carcinoma reaching the resection margins. Regarding DCIS, a distance of  $\geq 2$  mm from the margins is generally preferable [33].

The pathological prognostic stage [19] should be applied to patients treated with upfront surgery.

## 13.7 Treatment Approaches

BC treatment requires a multidisciplinary approach with different combinations of surgical intervention(s), radiotherapy, chemotherapy, hormonal therapy and targeted therapy. The optimal combination and sequence depends on the stage, biology of cancer and patient's preference. Before starting treatment and at relapse, it is important to discuss possible strategies both with a multidisciplinary BC team and with the patient.

### 13.7.1 Surgical Therapy

There are two main surgical options: breast-conserving surgery (lumpectomy, tumorectomy, quadrantectomy) and mastectomy. Both modalities try to accomplish two goals: excision of the lesion with clear margins and the best cosmetic result possible.

Breast-conserving surgery is now used for 60–80% of BCs [13]. Several techniques of oncoplastic surgery are currently used. In the case of large tumors, systemic therapy before surgery (neoadjuvant treatment) should be considered if a breast-conserving surgery seems attainable.

Indications for mastectomy are: large tumor size (relative to breast size), multicentricity, positive margins after prior breast-conserving surgery, contraindication

to adjuvant radiotherapy or patient choice [13]. Breast reconstruction after mastectomy can be immediate or deferred, use autologous tissue or implants, and is proved to improve quality of life [36]. There is no evidence that reconstruction makes detection of local recurrence more difficult. Contralateral mastopexy may be necessary to correct asymmetries [13].

In clinical node-negative disease, SLNB is the standard of care for axillary staging and is usually performed concomitantly with breast surgery. Technetium-labeled colloids and/or blue dye is injected in the tumor-site or near the nipple and accumulates in the draining LNs (SLNs), which are removed.

If a LN metastasis has been proven by biopsy or is clinically or radiologically suspected, axillary dissection is the standard of care. Axillary dissection is associated with morbidities, namely lymphedema (25% of women, one year postoperatively vs. <10% after SLNB, 15% after axillary radiotherapy only and 40% after axillary dissection and radiotherapy), recurrent seroma and neurological dysfunction [13].

### 13.7.2 Radiotherapy

Radiotherapy can be delivered to the tumor-site (partial breast irradiation), to the whole breast, to the chest wall (after mastectomy) and to the regional LNs (axilla, clavicular and/or internal mammary chain). Radiotherapy planning is used to minimize radiation of the heart, lung, glenohumeral joint and contralateral breast. Intensity modulated radiotherapy, when compared to conventional external beam radiotherapy, allows a more homogeneous dose distribution. The usual total dose for adjuvant therapy is 45–50 grays (Gy) in 25–28 fractions of 1.8–2.0 Gy. Shorter fractionation schemes, called hypofractionated radiotherapy (15–16 fractions with 2.5–2.67 Gy single dose), offer similar efficacy, safety and cosmetic results [13, 37].

After breast-conserving surgery, adjuvant whole breast radiotherapy reduces 5-year absolute risk of recurrence by 19% and 15-year absolute risk of BC death by 5.4% [38]. There is no subgroup of sufficiently low risk for whom radiotherapy can be omitted [39]. An additional boost dose (10–16 Gy) further reduces local recurrence by about one third [40]. The benefit was higher in women younger than 50 years, high-grade tumors and estrogen receptor-negative tumors [41].

After mastectomy, chest wall irradiation is the standard of care for patients with at least 4 metastatic LNs. For patients with 1–3 positive LNs or pT3–4 pN0 disease, chest wall irradiation should also be routinely considered [42].

Axillary radiotherapy for patients with one positive SLN and with tumors up to 5 cm was not inferior to axillary dissection (after a median follow up of 6 years) [43]. Lymphedema was more frequent with axillary dissection and shoulder motion disturbance was more frequent with radiotherapy.

Radiotherapy with or without hyperthermia is also an option for palliation of symptoms in advanced disease [16].

### 13.7.3 *Adjuvant Systemic Regimens*

The choice of the adjuvant regimens should be based on cancer biology, cancer stage and on patient's biological age, comorbidities and preferences. Adjuvant treatment is usually started between 2–6 weeks after surgery and delaying it more than 12 weeks post-surgery should be avoided [44].

Three decision-making tools (Adjuvant! Online, PREDICT and the Nottingham Prognostic Index) are validated to help predicting treatment-response and recurrence-risk [45–47]. Gene expression assays, where available, can also serve to predict the risk of recurrence and/or the benefit from adjuvant chemotherapy.

Luminal A-like tumors are mainly treated with ET. Adding chemotherapy should be considered in a minority of cases with higher stages. Luminal B-like tumors should receive ET and adjuvant chemotherapy must be considered [13].

There are multiple ET options (Fig. 13.2). Tamoxifen is a selective estrogen receptor modulator (SERM) that has an anti-estrogenic effect in breast tissue. Fulvestrant, only approved for advanced BC, is a selective estrogen receptor degrader (SERD). Aromatase inhibitors (AIs: exemestane, letrozole, anastrozole) inhibit the synthesis of estrogens from androgens outside the ovaries. Gonadotropin-releasing hormone (GnRH) agonists (goserelin, triptorelin and leuprolide) have a paradoxical effect when continually administered in premenopausal patients: by repeatedly binding to the GnRH receptor they lead to desensitization, decrease FSH/LH and, consequently, estrogen production by the ovaries, inducing a menopause-like condition [48].

All ETs may cause or worsen postmenopausal symptoms, including potentiating osteoporosis. Monitoring bone health, especially in women under AIs or GnRH agonists, is highly recommended. Tamoxifen also increases the risk of thromboembolism and, rarely, uterine cancer [16, 48].

For premenopausal women, adjuvant treatment with tamoxifen for at least 5 years is the standard of care. Continuation up to 10 years further reduces recurrence and increases OS, at the stake of prolonging tamoxifen's side effects. This should be considered for women with high stage tumors and adequate tolerance to tamoxifen [33, 49]. Combinations of tamoxifen and ovarian function suppression (OFS; as with GnRH agonists or bilateral oophorectomy) or an AI and OFS were shown to be superior to tamoxifen alone, especially in patients with an estimated high risk of recurrence or younger than 35 years old [50]. The combination of an AI (exemestane) and OFS has been proven to be more effective than tamoxifen combined with OFS in terms of disease-free survival [51]. It is noteworthy that GnRH agonists administered during adjuvant chemotherapy also have a role in preventing chemotherapy-related ovarian failure [52].

Postmenopausal women can be offered tamoxifen alone (for a selected low-risk group), an AI alone or a combination of both sequentially. Sequential regimens include tamoxifen for 2–3 years followed by an AI for another 2–3 years (for a total of 5 years) or reverse. Extended endocrine therapy (for more than 5 years) was shown to decrease the risk of recurrence especially in patients with higher risk of late recurrence, but the exact optimal duration is currently not defined [13, 53].

HER2-positive tumors are candidates for both chemotherapy and anti-HER2 antibodies. For patients with tumors with both HER2 overexpression and ER/PR positivity a double strategy (ET and anti-HER2 treatment) is indicated [13, 14].

Trastuzumab and pertuzumab are humanized monoclonal antibodies (mAbs) that bind, respectively, to the domains IV and II of the extracellular part of HER2. Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of trastuzumab and DM1, a microtubule-disrupting drug, that is validated only in the metastatic setting. Lapatinib and neratinib are oral tyrosine kinase inhibitors (TKI) that inhibit HER2/HER1's and HER2/HER1/HER4's kinases activity, respectively (Fig. 13.2) [22].

Standard of care for HER2-positive BC in the adjuvant setting consists of chemotherapy plus 12 months of trastuzumab [33]. Trastuzumab can induce cardiotoxicity, expressed by a decreased left ventricular ejection fraction and, rarely, cardiac failure. This is often asymptomatic and typically resolves after withdrawal. Therefore, in most centers, the cardiac function is monitored every 3 months. Trastuzumab is generally not combined with anthracyclines because of higher risk of cardiotoxicity [54].

For triple negative tumors, adjuvant chemotherapy stands as the only current strategy as there are no approved targeted therapies. The most frequent chemotherapy regimens for BC comprises a combination of anthracyclines and taxanes, with sequential use being preferred to concomitant use [13].

Worthy of mention, bisphosphonates were shown to reduce metastatic recurrence in the bone and improve BC specific survival in women with spontaneous or induced postmenopausal status [33, 55].

### 13.7.4 Neoadjuvant Regimens

Neoadjuvant treatment should be considered in locoregionally-advanced non-metastatic BCs. It decreases the extent of surgery needed and allows conversion to breast-conserving surgery in some cases. Also, it gives more time for surgery-planning, a chemosensitivity test and information on prognosis [13].

Imaging documentation of the lesion before and after neoadjuvant treatment, preferentially with MRI, is recommended [13]. Before neoadjuvant treatment, the tumor should be tagged with a radiopaque marker to ensure identification of the tumor bed after treatment.

When describing the TNM stage after neoadjuvant treatment a “y” is added as a prefix (ycTNM or ypTNM) [19]. Pathological complete response (pCR) means no residual tumor cells in the breast and lymph nodes after neoadjuvant therapy (ypT0 ypN0) and is an important prognostic factor [16].

All modalities discussed for the adjuvant setting may also be used preoperatively. For patients receiving neoadjuvant chemotherapy it is recommended to complete all planned cycles before surgery. The exception is capecitabine for patients with HER2-negative BC, who didn't reach pCR [56]. Anti-HER2 and/or ET started in the neoadjuvant setting can be continued after surgery [13, 14].

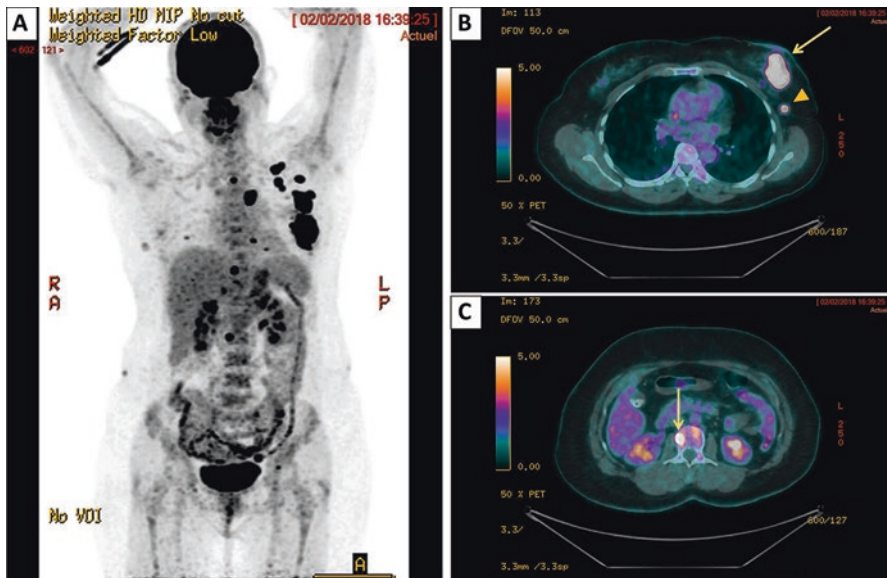
Neoadjuvant regimens for each surrogate intrinsic subtype are very similar to their adjuvant counterparts. Postmenopausal patients with ER-positive tumors may

benefit from preoperative tamoxifen or an AI for at least 6 months or until best response. In this setting, AIs appear to be more effective than tamoxifen in decreasing the extent of surgery needed [33, 57]. ET is not recommended preoperatively to premenopausal women due to paucity of studies [13].

In the case of HER2-positive tumors, adding pertuzumab or lapatinib to trastuzumab and chemotherapy significantly improves the pCR rate [33, 58]. For triple-negative tumors, adding a platinum compound to the traditional neoadjuvant scheme (taxanes and anthracyclines) can be considered, as it has been demonstrated to increase the pCR rate [33].

### 13.7.5 Metastatic Disease

Metastatic breast cancer (MBC) is generally an incurable disease with a median overall survival of 2–3 years and a 5-year survival of 25%. Approximately 20–30% of patients with initially early BC will develop metastasis. BC metastasizes preferentially to the bone, liver, lung, pleura, brain and distant lymph nodes (Fig. 13.7) [16, 59].



**Fig. 13.7** Metastatic breast cancer. (a) maximum intensity projection (MIP) showing multiple lesions in the left thorax and at least three central lesions; (b) Corresponding PET-CT scanner showing a hypermetabolic breast lesion (arrow) and a hypermetabolic lesion corresponding to a metastatic lymph node (arrow head); (c) Corresponding PET-CT scanner showing a hypermetabolic vertebral lesion (arrow) corresponding to a breast cancer metastasis

Patients with MBC will most likely receive anti-neoplastic therapies for almost all of the remaining lifetime with the goal of conserving quality of life and improving survival. This means dealing with disease symptoms, treatment-related adverse events, complex decision-making and the notion of an incurable disease. Patients can also face income-related and social problems. Careful thought must be given to ensure good communication and to encourage patient's involvement in decision-making. Psychological and social support should be offered [59].

A biopsy of the metastatic lesion can be considered if the confirmation of the diagnosis or the reassessment of the biomarkers can change strategy-choice. Treatment choice depends on cancer biology, disease burden, associated symptoms, kinetics of progression, previous therapies and patient's tolerance and preference [59].

If rapid disease control is needed, chemotherapy-based regimens are often considered. After achieving disease control and for maintenance, targeted therapies without chemotherapy or single-agent chemotherapy are preferred [59]. Treatment response should be assessed every 2–4 cycles for chemotherapy and every 2–3 months for ET, using the same imaging modality [16].

Patients with metastatic luminal tumors receive ET in the majority of cases. The exceptions are visceral crisis (rapid progression of disease and severe organ dysfunction as assessed by signs, symptoms and laboratory studies) and proven endocrine resistance (either primary or secondary/acquired) [59].

Recently, CDK4/6 inhibitors palbociclib, abemaciclib and ribociclib were approved in combination with AIs as first line treatments for luminal MBC as they significantly improve progression-free survival (PFS) with tolerable toxicity [60, 61]. Also, beyond 1st line ET, palbociclib combined with fulvestrant is an option for both post and premenopausal women (in combination with an GnRH agonist for the latter group of women) [61]. Currently, ribociclib and abemaciclib are only approved for postmenopausal women but ribociclib has recently proved to be effective in the premenopausal group [62]. Another option for this setting is the combination of ET with everolimus, a mTOR inhibitor. This combination has a PFS benefit with significant, but manageable, toxicity [59, 63]. Neither CDK4/6 inhibitors nor the mTOR inhibitor have shown an improvement in terms of OS so far.

For HER2-positive cancers, dual blockade with trastuzumab and pertuzumab combined with docetaxel provides significant OS and PFS benefit and is currently the standard 1st line therapy. Noteworthy, in the trial studying this combination about 90% of patients were previously untreated with trastuzumab in the (neo)adjuvant setting [59, 64]. Trastuzumab combined with other chemotherapy regimens is also a valid 1st line option. The continuation of trastuzumab beyond progression in association with other drugs proved to improve the outcome, but the optimal duration is unknown [59].

After progression under chemotherapy and trastuzumab, T-DM1 provides an OS benefit compared to the association of capecitabine and lapatinib. However, there is no randomized trial concerning the role of T-DM1 after dual blockade with trastuzumab and pertuzumab. The chemotherapy-free combination of trastuzumab and lapatinib is also a valuable option after progression on chemotherapy and trastu-

zumab. Still, no evidence exists regarding its efficacy after progression on pertuzumab or T-DM1 [59]. All patients should be considered for further anti-HER2 therapy even after relapse(s), except if there are contraindications [59].

Patients with triple negative disease are treated with sequential single-agent chemotherapy. Platinum compounds should be considered in the case of BRCA1/2-mutation. Combinations of chemotherapies is reserved for visceral crisis, symptomatic disease and rapid disease progression [59].

Among patients with HER2-negative MBC and a germline *BRCA* mutation, Olaparib, a poly-adenosine diphosphate-ribose polymerase (PARP) inhibitor, provided a significant PFS benefit over standard therapy with single-agent chemotherapy of the physician's choice [65].

### 13.8 Genetic Testing

*BRCA 1/2* mutations result in an increase in the order of 7 and 25 times the lifetime risk of breast and ovarian cancer, respectively. More than 90% of hereditary cases of breast and ovarian cancer are considered a result of one of these mutations. The estimated prevalence is 1/300 and 1/800 for *BRCA1* and *BRCA2* mutations, respectively [66].

Selection of patients for *BRCA* or other genetic testing can vary depending on local recommendations. Following appropriate genetic counseling, testing and diagnosis, prophylactic measures should be discussed.

### 13.9 Future Developments

An important breakthrough was recently made for luminal BC with the approval of CDK4/6 inhibitors based on an important improvement of the PFS. Results concerning OS are eagerly awaited [59]. PI3K, being a pivotal player in BC signaling and in the development of resistance, is a promising target with phase III studies ongoing [33].

Mutations of the ER can make it constitutively active even in the absence of a ligand and are a frequent event in pretreated MBC, causing resistance to AIs. Utilizing two inhibitors of the same pathway can lead to a synergic effect. A phase II study showed that the addition of everolimus to fulvestrant improves PFS in postmenopausal women with luminal MBC resistant to AI therapy [33, 67].

It is known that BC, especially HER2-like and triple negative BC, has significant interactions with the immune system. In triple negative BC, higher levels of tumor-infiltrating lymphocytes (TILs) at diagnosis are significantly associated with decreased distant recurrence rates. Several trials showed an activity of immune checkpoint inhibitors (namely pembrolizumab, atezolizumab and nivolumab) and T-cell therapies in triple negative BC. Earlier lines of treatment and the presence of



TILs are related to higher response rates [68, 69]. Several strategies, including combinations, are currently being studied in triple negative BC and in other BC subtypes.

Androgen receptors are often expressed in BC. Antiandrogen therapies are being studied with some efficacy data already available for triple negative BC with enzalutamide, bicalutamide, and abiraterone [70–72].

Other currently explored strategies include histone deacetylase inhibitors, which seem to reverse resistance to endocrine therapy [73].

### Key Messages

- **Epidemiology and risk factors:** BC is the most frequent cancer in women and the first cause of cancer death in women in most countries. Risk factors comprise female gender, advanced age, family history, breast density and hormonal factors.
- **Screening:** At least one mammography yearly to 3-yearly for women between 50 and 70 years old is recommended in screening programs. Before screening, a thoughtful discussion about the benefits and risks is imperative.
- **Diagnosis and staging:** After anamnesis and clinical examination, bilateral mammography and ultrasound of the breast and axilla are needed. A core needle biopsy of the breast lesion confirms the diagnosis.
- **Molecular pathways:** Main predictive factors are ER, PR, HER2, Ki67, BRCA1/2 and PI3K. HER2 overexpression occurs mainly due to *ERBB2* gene amplification and, less frequently, mutation. PI3K is a pivotal player in BC. The cD1/CDK4/6 pathway is particularly active in ER-positive BC and promotes proliferation.
- **Pathology:** Pathological assessment describes namely histological type, grading and biomarker status (ER, PR, HER2 and Ki67). Invasive BC is divided in NST and special type. DCIS is a pre-neoplastic lesion while LCIS is a risk factor for invasive BC. There are four surrogate intrinsic subtypes: Luminal A-like, luminal B-like, HER2-like and triple negative.
- **Surgical therapy:** BC surgery aims at an oncologically correct excision with the best cosmetic result. Breast-conserving surgery is now more frequent than mastectomy. SLNB and axillary dissection have advantages and disadvantages that should be discussed.
- **Radiotherapy:** Intensity modulated radiotherapy should be preferred to conventional external beam radiotherapy. The usual dose for adjuvant therapy is 45–50 grays Gy. After breast-conserving surgery, whole breast radiotherapy is indicated. After mastectomy, chest wall irradiation is indicated if  $\geq 4$  metastatic LNs. Axillary radiotherapy is preferable to axillary dissection if one positive SLN.
- **Adjuvant treatment:** Adjuvant treatment is usually started between 2 and 6 weeks after surgery. More frequently, luminal A-like tumors are treated with ET, luminal B-like tumors with ET and chemotherapy, HER2-like lesions with anti-HER2 treatment and chemotherapy and triple negative cancers with chemotherapy.

- **Neoadjuvant treatment:** Should be considered in locally-advanced non-metastatic BCs. A pCR is an important prognostic factor. Neoadjuvant regimens are similar to their adjuvant counterparts.
- **Metastatic breast cancer:** BC metastasizes preferentially to the bone, liver, brain and distant lymph nodes. Chemotherapy-based regimens are needed for rapid disease control. For maintenance, targeted therapies or single-agent chemotherapy should be preferred.
- **Genetic testing:** More than 90% of hereditary cases of BC are considered a result of *BRCA 1/2* mutations. Following appropriate genetic counseling and diagnosis, prophylactic measures should be discussed.

### Multiple Choice Questions

1. Concerning BC screening, select the incorrect statement:
  - (a) Reducing smoking, alcohol consumption, radiation exposure and obesity are part of BC primary prevention.
  - (b) Screening programs propose at least one mammography yearly to 3-yearly for women between 50 and 70 years.
  - (c) For women with high risk genetic predisposition annual MRI concomitantly or alternating every 6 months with mammography, is recommended.
  - (d) Mammography has a sensibility and specificity of 95%.
  - (e) Before screening, the risk of investigations related to false-positive results and overdiagnosis should be discussed.
2. Concerning BC diagnosis, select the correct statement:
  - (a) Whole body imaging is imperative to breast cancer staging.
  - (b) When examining the nipple-areola complex, retraction, inversion or an eczema-like rash are possible signs of breast cancer.
  - (c) Conception plans are not one of the priorities when initially diagnosing breast cancer.
  - (d) In the presence of clinically or ultrasound suspicious lymph nodes, a sentinel lymph-node biopsy should be performed.
  - (e) Preoperative pathological assessment of the primary lesion is the gold standard by fine-needle aspiration.
3. For a tumor with an immunophenotype of ER 90%, PR 80%, HER2 score 1+ and Ki67 15% and a histological grade 1, what is the surrogate intrinsic subtype?
  - (a) Luminal A-like.
  - (b) Basal-like.
  - (c) Luminal B-like.
  - (d) HER2-like.
  - (e) None of the above.
4. Regarding BC biomarkers, select the incorrect statement:

- (a) Ki67 can be a predictive factor for neoadjuvant chemotherapy response.
  - (b) HER2 expression is a factor of poor prognosis and a predictive factor of anti-HER2 treatment response.
  - (c) pCR is an important prognostic factor after neoadjuvant treatment.
  - (d) PR expression is not a prognostic factor.
  - (e) Histological grade is a prognostic factor.
5. Select the correct statement:
- (a) NST breast carcinoma was previously known as invasive ductal carcinoma and presents a homogeneous histology.
  - (b) The immunophenotype of mucinous carcinomas is frequently triple negative.
  - (c) Metaplastic carcinomas have a bad prognosis and are frequently triple negative.
  - (d) LCIS is a precursor of invasive breast cancer.
  - (e) Lobular carcinoma is frequently multicentric and has preserved expression of E-cadherin in the majority of cases.
6. Select the incorrect statement:
- (a) The histological grade relies on the evaluation of tubule formation, nuclear pleomorphism and mitotic count and goes from G1 to G3.
  - (b) When evaluating residual tumor burden, a distance of 2 mm from the invasive carcinoma to the resection margin is considered a R1.
  - (c) Multigene tests (Mammaprint® and Oncotype®) can have predictive value.
  - (d) The pathway cD1/CDK4/6 is particularly active in ER-positive breast cancers and promotes proliferation.
  - (e) *PIK3CA* mutations are not rare in breast cancer.
7. Regarding surgical options for breast cancer, select the correct statement:
- (a) A patient with a diagnosis of DCIS only is not a surgical candidate.
  - (b) Tumor size, multicentricity, contraindication to radiotherapy, positive margins after prior resection or patient choice are indications for mastectomy.
  - (c) Nowadays in developed countries it is possible to perform breast-conserving surgery in approximately half of the patients.
  - (d) Axillary dissection is associated with lymphedema of the arm, while axillary radiotherapy and SLNB are innocuous from this point of view.
  - (e) There is evidence that reconstruction makes detection of local recurrence more difficult.
8. Identify the incorrect statement regarding radiotherapy for breast cancer:
- (a) The usual total dose for adjuvant therapy is 45–50 Gy in 25–28 fractions or 15–16 fractions.
  - (b) After breast-conserving surgery, there is no subgroup of sufficiently low risk for whom radiotherapy has no benefit.

- (c) Radiotherapy with or without hyperthermia is an option for palliation of symptoms.
  - (d) For a patient with one positive SLN and a small tumor, axillary dissection is the standard of care but axillary radiotherapy can be discussed.
  - (e) For a patient with two positive LN after mastectomy and axillary dissection, chest wall irradiation is the standard of care.
9. Concerning endocrine therapies for breast cancer, select the correct statement:
- (a) Tamoxifen is a selective estrogen receptor degrader.
  - (b) Fulvestrant is a selective estrogen receptor modulator that has an anti-estrogenic effect in breast tissue.
  - (c) Goserelin, triptorelin and leuprolide are GnRH antagonists.
  - (d) Aromatase inhibitors inhibit all steps of estrogen biosynthesis.
  - (e) Endocrine therapies can cause or worsen menopausal symptoms and potentiate osteoporosis.
10. Concerning breast cancer treatment, select the incorrect statement:
- (a) Standard of care for HER2-positive BC consists of chemotherapy plus 12 months of trastuzumab.
  - (b) For patients with tumors with both HER2 overexpression and ER/PR positivity a double strategy (ET and anti-HER2 strategies) is indicated.
  - (c) Trastuzumab's cardiotoxicity manifests more frequently as an asymptomatic decrease of left ventricular ejection fraction.
  - (d) Tumors with a low percentage of tumor cells expressing Ki67 respond better to chemotherapy.
  - (e) The most frequent chemotherapy regimen for triple negative BC is a sequential use of an anthracycline and a taxane.
11. Regarding neoadjuvant treatment, select the incorrect statement:
- (a) Neoadjuvant treatment is not an option for metastatic breast cancer.
  - (b) Neoadjuvant treatment is an indication for pre and post-treatment imaging, preferably with an MRI.
  - (c) A patient with a tumor classified as ypT0 ypN0 cM0 has already received neoadjuvant treatment and presents a pathological complete response.
  - (d) Neoadjuvant chemotherapy cycles should be distributed in an equitable manner before and after surgery.
  - (e) Combining the two anti-HER2 mAbs pertuzumab and trastuzumab is not redundant.
12. Concerning metastatic breast cancer, select the incorrect statement:
- (a) Visceral crisis defines the rapid progression of disease and severe organ dysfunction as assessed by imaging and laboratory studies.
  - (b) When diagnosing the first breast cancer metastasis, a biopsy of the lesion should be considered.
  - (c) For visceral crisis, chemotherapy regimens are usually the most effective.

- (d) Treatment response should be assessed every 2–4 cycles for chemotherapy and every 2–3 months for ET, using the same imaging modality.
- (e) Regimens of targeted therapies without chemotherapy or single-agent chemotherapy should be preferred.
13. For a postmenopausal patient with an initial diagnosis of a Luminal A-like, pT3 pN2 cM0 breast cancer, previously treated with tamoxifen for 5 years, that presents with a proven lung metastasis, which of the following options would be a possible treatment choice:
- (a) A regimen with taxanes and an endocrine therapy.
- (b) A chemotherapy-free combination of trastuzumab and lapatinib.
- (c) Palbociclib combined with anastrozole and goserelin.
- (d) Palbociclib combined with everolimus.
- (e) Palbociclib combined with fulvestrant.
14. For a patient with HER2-like, pT2 pN0 cM1 breast cancer, that relapses after trastuzumab and pertuzumab in the metastatic setting, with no contraindications to anti-HER2 treatment, which is the best option:
- (a) Single-agent chemotherapy.
- (b) Multi-agent chemotherapy.
- (c) Palbociclib combined with anastrozole.
- (d) T-DM1.
- (e) A combination of trastuzumab and T-DM1.
15. Regarding genetic counseling, select the incorrect statement:
- (a) *BRCA 1/2* mutations increase the lifetime risk of breast and ovarian cancer.
- (b) About 95% of the cases with genetic predisposition are a result of *BRCA* mutations.
- (c) Male breast cancer, bilateral breast cancer and a known mutation in a cancer susceptibility gene within the family are some of the prompting factors for genetic testing.
- (d) The estimated prevalence is 1/300 and 1/800 for *BRCA1* and *BRCA2* mutations, respectively, in the general population.
- (e) After genetic counseling and testing with a positive result, prophylactic measures should be discussed.

### Answer

1. (d).
2. (b) In developed countries, 90% of BCs are locoregional when first diagnosed and asymptomatic distant metastases are very rare. Paget's disease of the breast associates with invasive or in situ carcinoma in approximately 90% of patients. A core biopsy is needed for the preoperative pathological assessment.
3. (a).
4. (d) PR expression is a predictive factor for ET response.

5. (c) LCIS is considered a risk factor and not a precursor for the development of subsequent invasive cancer in either breast, of either ductal or lobular types.
6. (b) R1 is defined as invasive carcinoma reaching the resection margins.
7. (b).
8. (e) After mastectomy, for patients with 1–3 positive LNs or pT3-4 pN0 disease, chest wall irradiation should also be routinely considered.
9. (e).
10. (d) High Ki67 expression is a predictive factor for chemotherapy response.
11. (d) Neoadjuvant chemotherapy should be completed before surgery and no further chemotherapy should be given after.
12. (a) Visceral crisis is a rapid progression of disease and severe organ dysfunction demonstrated by signs, symptoms and laboratory studies.
13. (e).
14. (d) Trastuzumab should be continued beyond progression but the optimal duration is unknown.
15. (b)

### Clinical Case

A premenopausal 39-year-old woman accepts to undergo screening mammography for the first time after a discussion with her family doctor. A spiculated lesion with microcalcifications is found on the upper outer quadrant of the left breast. A breast ultrasound confirms the presence of an hypoechoic lesion of approximately 2.5 cm. No suspicious ganglia were found at physical examination or with axillary ultrasound. A core biopsy diagnoses an invasive carcinoma of NST, grade 3 according to the Elston and Ellis grading system, ER 0%, PR 10%, Ki67 50% and an ambiguous HER2 score (2+). The ISH analysis concludes a *HER2*/chromosome 17 ratio of 2.

After communication of the results and discussion the patient decides for a left mastectomy. The pathological evaluation of the surgical piece reveals a 3 cm invasive carcinoma of NST, grade 3, ER 0%, PR 5%, Ki67 60% and an HER2 score 3+. A SLNB is also performed. TNM stage (8th edition) is defined as pT2 pN1a(sn) (1/3) cM0 R0.

1. What would be a possible adjuvant treatment-choice?
  - (a) An anthracycline for 6 months and trastuzumab for 1 year.
  - (b) A taxane for 6 months, trastuzumab for 1 year and axillary radiotherapy.
  - (c) A combination of anthracyclines and taxanes and chest wall irradiation.
  - (d) Ovarian function suppression and tamoxifen for 5–10 years.

A cardiac ultrasound is performed before beginning the treatment (left ventricular ejection fraction (LVEF) of 60%) and every 3 months. Six months after the beginning of adjuvant treatment, an asymptomatic LVEF of 43% is found.
2. What would be the correct approach?
  - (a) Pursue the treatment as planned and evaluate LVEF in 3 months.
  - (b) Withdraw trastuzumab and pursue the chemotherapy regimen for another 6 months.

- (c) Withdraw trastuzumab, evaluate LVEF in 3 weeks and consider asking for a cardiologist's input.
- (d) Withdraw trastuzumab and start pertuzumab.

Three weeks after withdrawal of trastuzumab, LVEF was measured at 53%. Rechallenge with trastuzumab was well tolerated and allowed completion of the 12 months.

Three years after the initial diagnosis, the patient presents lymphedema of the left arm and left hip pain. A PET-CT shows a hypermetabolic lesion of the left sacro-iliac joint. A biopsy confirms stage IV disease.

3. Which would be a reasonable choice (you may choose more than one answer)?
  - (a) Discuss starting a combination of trastuzumab, pertuzumab and docetaxel with the multidisciplinary team.
  - (b) Single agent chemotherapy.
  - (c) T-DM1.
  - (d) A combination of trastuzumab and chemotherapy.

### Answer

1. (b).
2. (c) For in-depth information see Curigliano, et al. "Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines." *Annals of Oncology*, 2012 [74].
3. (a and d).

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# Chapter 14

## Esophageal Cancer



**Karima Oualla, Nawfel Mellas, Luis Castelo-Branco,  
and Ramon Andrade De Mello**

**Abstract** Esophageal cancer is one of the most virulent digestive malignancies and a leading cause of cancer-related mortality worldwide.

The SCC subtype is more frequent, but adenocarcinoma has become the leading histological subtype in Western countries, due to the increase in the incidence of obesity, gastro-esophageal reflux disease and Barrett's esophagus.

An accurate pre-treatment staging plays a crucial role in guiding therapeutic strategy and has a great impact on erc prognosis.

Treatment requires a multidisciplinary team approach for two main axes: locoregional treatment and systemic therapy. For locoregional treatment, surgery plays an important role in achieving local control and offers the best chance for cure in localized and locally advanced disease, especially with new techniques. Radiotherapy alone or in association with chemotherapy, plays also a major role as a locoregional

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therapeutic option. In metastatic setting, and with the lack of specific targeted therapies for esophageal cancer, conventional chemotherapy remains the mainstay of treatment in addition to best supportive care with suboptimal outcomes. The recent knowledge on biomolecular alterations and identification of new targets are allowing the development of promising targeted therapeutic agents for esophagus cancer.

**Keywords** Esophagus · Adenocarcinoma · Squamous cell carcinoma · Epidemiology · Diagnosis · Multimodal treatment

## Abbreviations

BE	Barett's esophagus
CF	Cisplatin-5FU
COX	Cyclo-oxygenase
CT	Computed tomography
CTLA-4	Cytotoxic T lymphocyte antigen associated 4
DCF	Docetaxel-cisplatin-5FU
dMMR	deficient Mismatch repair deficient
EAC	Esophageal adenocarcinoma
ECF/ECX	Epiribucin – cisplatin –5-FU or capecitabine
EGJ	Esogastric junction
EGFR	Epidermal growth factor
EUS	endoscopic ultrasound
FAMTX	5FU-adryamycin-methotrexate
FDG-PET	Fluorodeoxyglucose Positron emission tomography
FLOT	5-FU- leucovorin-docetaxel-oxaliplatin-docetaxel
GERD	gastroesophageal reflux disease
HER 2	human epidermal growth factor receptor 2
HP	Helicobacter Pylori
HPV	Human papilloma virus
MSI-H	Microsatellite instability-high
NSAID	Nonsteroidal anti-inflammatory drug
OS	Overall survival
PD1	Program death 1
PDL1	Program death ligand 1
PTEN	Phosphatase and tensin homolog
RT	Radiotherapy
SCC	Squamous cell carcinoma
VEGF	Vascular endothelial growth factor

## 14.1 Introduction

Esophageal cancer is a highly aggressive and fatal malignancy, with an increasing incidence and poor 5-years overall survival not exceeding 20% [1]. At the time of diagnosis more than 50% of patients are metastatic and around 30% have a locally advanced disease [2–4].

The disease has largely evolved over last years from predominantly SCC features to those of adenocarcinoma [5]. Multimodal treatment, including surgery, chemotherapy, and radiotherapy is required for most patients after an evaluation in a multidisciplinary approach. Several trials are ongoing to develop novel arsenal of therapeutic options in esophageal cancer.

## 14.2 Anatomy

The esophagus is a muscular conduit serving as gastrointestinal tract for food, connecting thorax with stomach. It has different tissue layers- mucosa, submucosa, muscularis externa, and adventitia. It extends from the level of the 7 cervical vertebra to the 11 thoracic vertebra, and is surrounded by a rich network of lymphatic channels which drains longitudinally along the submucosa [6].

Esophagus tumors are described by endoscopy in terms of distance of the upper border of the tumor to the incisors teeth. Subsequently, the esophagus is divided into four segments: cervical esophagus (5–20 cm from the incisors), upper thoracic esophagus (20–25 cm from the incisors), middle thoracic esophagus (25–30 cm from the incisors) and lower thoracic esophagus and gastroesophageal junction (30–40 cm from the incisors).

## 14.3 Epidemiology

### 14.3.1 *Descriptive: Incidence and Mortality*

Esophageal cancer is the eighth most common cancer worldwide, and the sixth most common cause of cancer related deaths [7]. Its incidence has known an increase over past decades.

The highest rates were reported in Eastern Asia and Southern and Eastern Africa, while the lowest rates in Western and Middle Africa and Central America [8]. Esophageal squamous cell carcinoma (SCC) is the predominant histological subtype worldwide especially in the highest-risk area, called the “esophageal cancer belt” including Northern Iran, the central Asian countries and to North-Central China where it accounts around 90% of cases [9, 10].

The epidemiology of esophageal cancer has known a significant switch in Western countries with a decrease in SCC at the expense of an important increase in the incidence of adenocarcinoma of the distal esophagus and the esophagogastric junction [11].

**Table 14.1** Risk factors of squamous cell carcinoma and adenocarcinoma of the esophagus

Risk factors	adenocarcinoma	Squamous cell carcinoma
Geography	Western Europe, North America, Australia	Southeastern Africa, Asia, Iran, South America
Gender	Male >> female	Male > female
Race	White > black	Black > white
Tobacco	+	++++
Alcohol	–	+++
High BMI	+++	–
GERD/BE	++++	–
N-nitroso components	–	+++
High temperature beverages and foods	–	++
Areca nuts	–	++
Diet: Low fruits and vegetables	+	++
HPV	–	++
Genetic aspects	+	++

*BMI* Body mass index, *HPV* Human papilloma virus, *GERD* Gastroesophageal reflux disease, *BE* Barrett's esophagus

## 14.3.2 Analytic: Risk Factors (Table 14.1)

### 14.3.2.1 Race and Gender

Worldwide, SCC is 2–3 times more frequent in males than females and this gender difference is even more marked in adenocarcinoma subtype [12].

In the United States of America (USA), adenocarcinoma was reported mainly in white males and recent registry study confirmed these findings by reporting an incidence of 4.87 per 100,000 among white men and an incidence of 0.68 per 100,000 among white women [13].

Regarding histological subtype, SCC is the most frequent histological type in black individuals and Asians while adenocarcinoma is largely a disease of Caucasians.

The incidence of EAC is 4–5 times higher in Caucasians comparing to African-Americans, Asians in the USA [14].

### 14.3.2.2 Genetic Factors

The influence of hereditary factors in esophageal cancer remains uncertain, but the familial aggregation has been described especially in regions with a high incidence of esophageal SCC [15]. Some hereditary conditions were reported to increase the risk of developing esophageal cancer including germline mutations in the tumor suppressor gene *PTEN* and the Peutz-Jeghers syndrome [16]. Tylosis is also a rare disease that has been strongly linked to esophageal SCC [17]. Deletions in a tumor

suppressor gene mapped to chromosome 17q25.1 were found to occur in 70% of patients with SCC [17].

#### **14.3.2.3 Smoking and Alcohol**

Smoking and alcohol consumption are major risk factors for esophageal SCC and may have a synergistic effect on increasing the relative risk [18]. Their confirmed role in the carcinogenesis of other aerodigestive cancers such as lung and head and neck cancers justifies the need of exploring possible synchronous association during the diagnosis.

#### **14.3.2.4 Dietary Factors**

Several dietary factors were found to be linked to esophageal cancer especially the SCC. Foods containing N-nitroso components have been associated with high incidence of SCC particularly in high-risk endemic areas [19, 20].

Chewing of areca nuts which is common in Southeast Asia and India also was associated with the development of SCC [21].

High temperature beverages and foods may increase were also reported to be risk factors by the thermal injury caused to the esophageal mucosa [22].

Other dietary factors were reported especially in endemic regions for SCC, such as high intake of red meat, low intake of fruits, vegetables and folate [23, 24].

#### **14.3.2.5 Human Papillomavirus**

The association between Human papillomavirus (HPV) and risk of esophageal SCC cancer has been widely investigated in several studies by analogy with its evident role in head and neck carcinomas and they have shown that HPV infection was associated to esophageal SCC in 11.7–38.9% of cases [25]. The most frequently detected stereotypes of HPV were 16 and 18 with more significant association with SCC for HPV16 [26]. HPV seems to be an important risk factor for esophageal SCC, but the evidence for a confirmed etiological role was not as strong as that observed for cervical and oropharyngeal carcinomas.

#### **14.3.2.6 Gastroesophageal Reflux Disease (GERD) and Barret's Esophagus (BE)**

Esophageal adenocarcinomas arise frequently from esophageal epithelium that was replaced by metaplastic columnar cells (Barret's esophagus) due to chronic gastroesophageal reflux disease (GERD).

A large study has shown that reflux symptoms were associated with esophageal adenocarcinoma (odds ratio 7.7) with higher risk among patients with long-standing (>20 years) and severe symptoms [27].



Patients diagnosed with Barret's esophagus (BE) have an increased risk of developing esophageal cancer and this risk becomes higher when high-grade dysplasia is found.

#### 14.3.2.7 Obesity and Metabolic Syndrome

Obesity has a crucial and consistent role in the development of esophageal adenocarcinoma while it does not appear to increase the risk of SCC.

The rapid rise of obesity in the western countries was parallel to the increase of incidence of esophageal adenocarcinoma (EAC) and also to Barrett's esophagus [28]. For patients with BMI of 30 or more, the risk of EAC is approximately 16 times greater compared to those with a BMI of 22 or less [29].

#### 14.3.2.8 Drugs

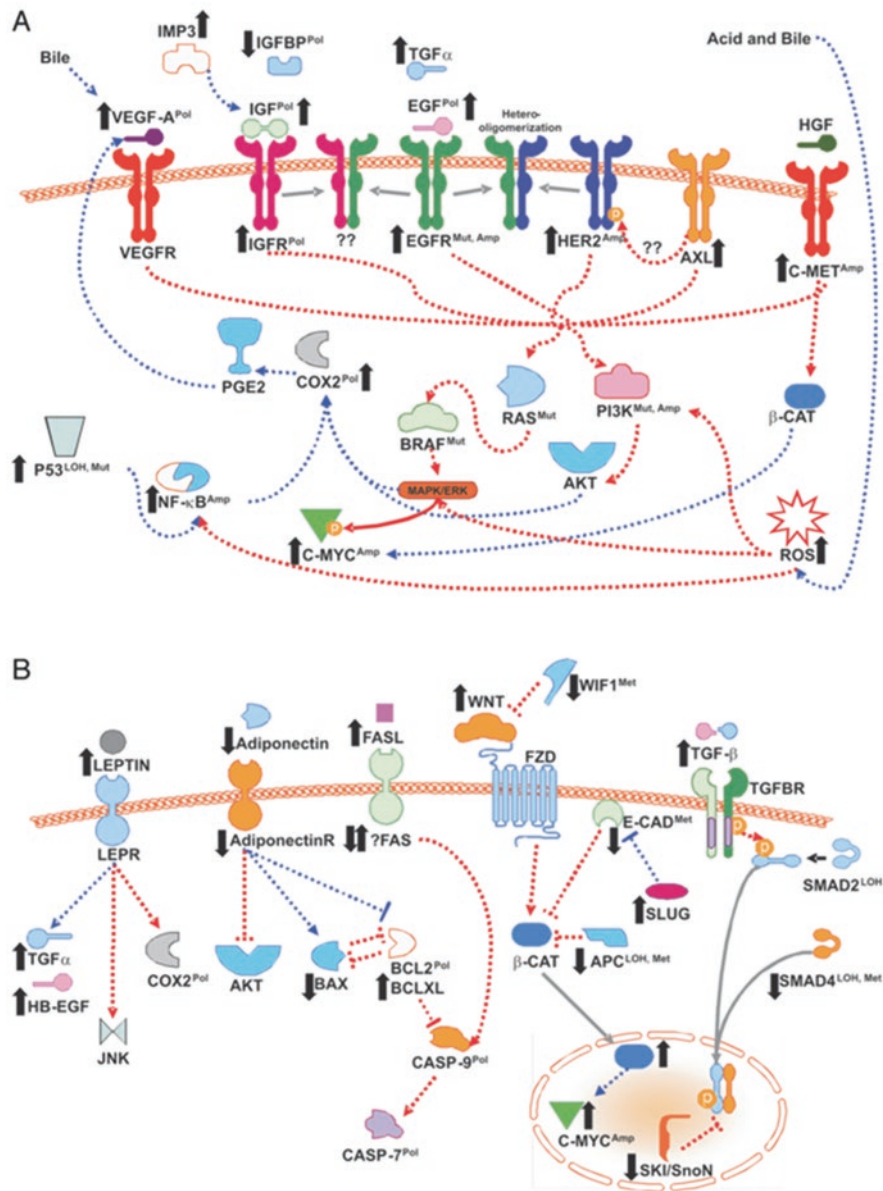
Epidemiologic data suggest that aspirin and other Nonsteroidal anti-inflammatory drug (NSAIDs), which inhibit cyclooxygenase (COX), might protect against development of esophageal cancer, particularly in the setting of Barrett's esophagus [30]. Several studies showed a significantly lower risk of EAC among patients who routinely consume aspirin or NSAID, compared to nonusers [31].

### 14.4 Molecular Mechanisms

Molecular profiling confirmed the heterogeneous nature of esophageal cancer that had already been observed from its clinical behavior. The Cancer Genome Atlas (TCGA) Research Network analyzed primary esophageal cancer and identified significant molecular differences between the two main subtypes (Figs. 14.1 and 14.2).

The comparison between the genomic alterations of 164 esophageal cancers and 359 gastric cancers and 275 head and neck cancers was studied and the results revealed more common features between esophageal SCC and head and neck SCC which do not stem from HPV infection, than with esophageal adenocarcinomas. Similarly, esophageal adenocarcinoma has more common features with gastric cancers particularly characterized by **chromosomal** instability, called the CIN subtype. The molecular analyses also showed that SCC showed frequent genomic amplifications of CCND1 and SOX2 and/or TP63, whereas ERBB2, VEGFA and GATA4 and GATA6 were more commonly amplified in adenocarcinomas [32].

The study found some other important genomic alterations including on genes that regulate the cell cycle. Therefore, grouping esophageal cancers based on their molecular underpinnings may lead to the improvement of prevention, diagnosis, and treatments.



**Fig. 14.1** Signalling pathways in development of esophageal adenocarcinoma. (a) Receptor tyrosine kinase. (b) Non receptor tyrosine kinase

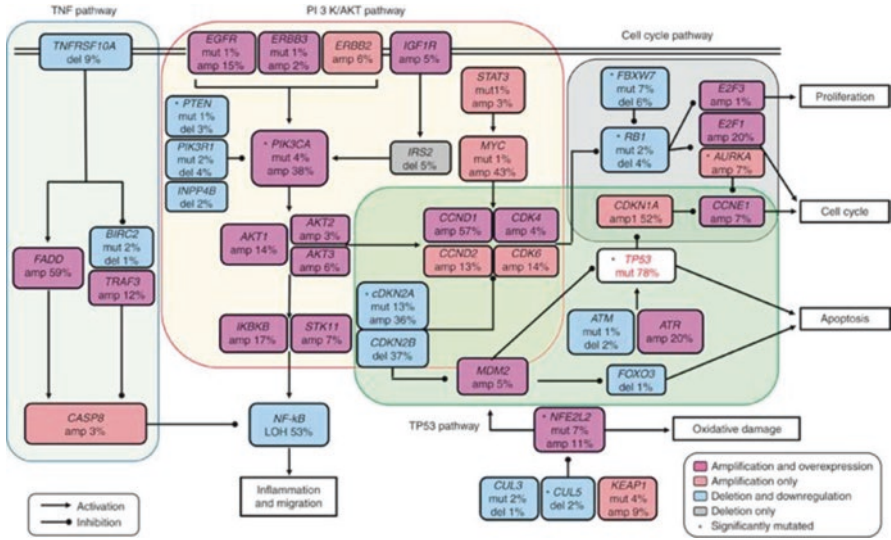


Fig. 14.2 Signalling pathways in squamous cell carcinoma (SCC)

## 14.5 Diagnosis and Staging

### 14.5.1 Clinical Presentation

Early stages of esophageal cancer may be asymptomatic or with nonspecific symptoms. Patients may present retrosternal discomfort or a burning sensation and may precede dysphagia which gradually progresses from solids to liquids [33].

Patients with advanced thoracic or cervical esophageal carcinoma usually present with progressive dysphagia, often accompanied by weight loss. Chronic gastrointestinal blood loss from esophageal and esophagogastric junction (EGJ) cancer is common and may result in anemia [34].

Esophageal cancer may be diagnosed at advanced stage with complications such as tracheobronchial fistulas which are observed in late stages. Patients may also present symptoms related to distant metastatic disease in liver, lungs, bone, or adrenal glands.

### 14.5.2 Work up

The histological confirmation of esophageal cancer is required. The diagnostic biopsy may be obtained by upper endoscopy or, if metastases are present, by biopsy of a metastatic site.

Endoscopy is the gold standard for the diagnosis of esopharyngeal cancer. It allows to identify tumor location and length in addition to performing biopsies for

histological examination [35]. Once the histological diagnosis is confirmed, the clinical staging should be established by the evaluation of locoregional disease extent and distant metastases in order to select the appropriate therapeutic strategy and define the prognosis which is closely associated with disease stage [35].

Computed tomography (CT) with contrast of the neck, chest and abdomen is the first staging exam to perform that appreciates the extension to adjacent structures but it is less accurate regarding early stage esophageal cancer [36]. It also has high sensitivity and specificity in detecting mediastinal invasion ranging between 85% and 100% [36].

The CT scan is more contributive in terms of identification of distant metastases which are more intraabdominal for adenocarcinomas and more intrathoracic for SCC [37].

Regarding locoregional evaluation, endoscopic ultrasound (EUS) is the preferred tool for the evaluation of T stage with high sensitivity and specificity rates reaching 92, and 97% respectively. Its contribution increased in advanced stages (T3, T4) rather than early stage (T1). Another role of EUS is the achievement of locoregional lymph node staging of esophageal cancer by imaging characteristics and guide for fine needle aspiration (FNA), when needed for histological confirmation [38].

For cervical SCC, laryngoscopy is recommended to exclude synchronous malignancy of the head and neck, while bronchoscopy is indicated for patients with a thoracic esophageal cancer at or above the carina [39].

Fluorodeoxyglucose (FDG) – Positron-emission tomography (PET) scan provides useful information about potential metastatic disease especially in patients who are candidates for curative surgery [40, 41]. Another role of PET/CT is the assessment of response after neoadjuvant treatment.

Staging laparoscopy is an option for patients with distal esophageal and EGJ adenocarcinomas with no evidence of distant metastases and who are potential candidates for curative resection or in case of suspicious intraperitoneal metastatic lesions that cannot be confirmed by other preoperative imaging [42].

Brain imaging is not recommended routinely unless there are suspicious symptoms of brain metastases [39].

## 14.6 Classification

The tumor, node, metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) for esophageal cancer is used universally [43]. Cancers that involve the EGJ with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal cancer and independently of histological subtype, all esophageal tumors have the same criteria for TNM staging and differentiation grading (Tables 14.2 and 14.3).

**Table 14.2** Esophagus and esophagogastric junction cancers TNM staging AJCC UICC 2017

Category	Criteria
<b>T category</b>	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a*	Tumor invades the lamina propria or muscularis mucosae
T1b*	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a*	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b*	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
<b>N category</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
<b>M category</b>	
M0	No distant metastasis
M1	Distant metastasis

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**Table 14.3** Histologic grade of esophageal cancers (SCC and adenocarcinoma)

**GX:** The grade cannot be assessed. (The grade is unknown).

**Grade 1: Well differentiated** means the cancer cells look more like normal esophagus tissue.

**Grades 2: Moderately differentiated** falls somewhere in between G1 and G3.

**Grade 3: Poorly differentiated, undifferentiated** means the cancer cells look very abnormal.

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## 14.7 Pathology

Esophageal cancers histology are dominated by SCC and adenocarcinoma. Other subtypes are very rare such as lymphomas, carcinoids, sarcomas or small cell carcinomas [44].

SCC occurs most commonly in the middle third of esophagus followed by lower one-third and upper one-third respectively. It is defined as an invasion of neoplastic squamous cells into lamina propria and deeper layers. SCC may be preceded by squamous dysplasia or Intraepithelial neoplasia which is a precursor lesion [45].

Histologically, SCC may have variable differentiation including well, moderately and poorly differentiated carcinomas.

Esophageal adenocarcinoma occurs commonly in the distal esophagus and the esophagogastric junction. It is a carcinoma with glandular differentiation and tubular, tubulopapillary or papillary growth pattern, that frequently arises in the setting of Barrett's esophagus [46]. It might follow the progression of intramucosal adenocarcinoma which is defined by invasion of carcinoma into lamina propria.

The adenocarcinoma subtype also shows variable grades of differentiation based on the amount of gland formation, and the nuclear atypia.

## 14.8 Treatment Approches

An accurate staging is mandatory to guide therapeutic strategy for esophageal cancer, which must be done by a multidisciplinary team [47].

The treatment depends mainly on the stage of the disease, tumor location, and patients medical fitness. The different therapeutic options followed mainly 2 axes: locoregional treatment and systemic therapies.

Surgery is still the mainstream curative treatment for esophageal cancer in localized and locally advanced disease [48].

The considerable rates of relapses, the poor long-term outcomes of patients after surgical treatment alone and the high sensitivity to chemotherapy and radiotherapy have prompted the evaluation of neoadjuvant, adjuvant, and non-surgical strategies that aim to improve survival in patients with non metastatic disease [49].

In metastatic setting, the main objective is to improve the quality of life for patients with palliation of symptoms. The addition of chemotherapy to best supportive care depends mainly on patients' performance status. Another important option is enrollment of patients in a clinical trial if available.

## **14.8.1 *Locoregional and Locally Advanced Disease***

### **14.8.1.1 Endoscopic Treatment**

The standard treatment for superficial esophageal cancer including carcinoma in situ and T1 Tumors, has been for a long time esophagectomy with achievement of good results in terms of survival but with high rates of morbidity. These findings have encouraged the development of endoscopic approaches including endoscopic mucosal resection, radiofrequency ablation, cryotherapy, and photodynamic therapy in patients with superficial cancers that involve only the mucosa with low risk of developing lymph node metastases or who are not fit for surgery [50].

Patients with an apparently superficial esophageal cancer must undergo an EUS to assess the depth of invasion with endoscopic resection. If endoscopic examination shows submucosal invasion or lymph node involvement, the esophagectomy will be the appropriate treatment [51, 52].

### **14.8.1.2 Surgical Treatment**

Esophagectomy is the gold standard for localized esophageal cancer without distant metastatic disease or invasion of unresectable structures [53]. It may be indicated upfront for tumors staged T1-T2 N0 M0, or after neoadjuvant treatment with chemotherapy or chemoradiotherapy in patients with thoracic esophageal or esophagogastric junction tumors and full-thickness involvement of the esophagus (T3) [53]. Also, in some selected patients with T4a disease and invasion of local structures, but who are candidates for curative resection, esophagectomy could be performed [53].

In localized disease, complete surgical resection alone provides better results vs medical treatment alone with 5 years survival of 28% vs 10% respectively [54–56]. But multi-modality treatments showed better results, as shown below.

Patients with middle or lower third of the esophagus cancer, regardless of histology, generally undergo a total esophagectomy because of the risk of submucosal skip lesions [57].

For patients with cervical esophageal cancer who frequently present with an advanced stage, they may require a larger surgical resection extended to adjacent structures.

The transhiatal, Ivor-Lewis (transthoracic), and tri-incisional esophagectomy techniques are widely performed in North America while an esophagectomy with an extended three-field lymphadenectomy (3FLD) is commonly performed in Asia [58–60].

Several studies have demonstrated the superiority of 3FLD as compared 2FLD but is not considered a standard technique in Western countries. Therefore, for patients with a thoracic esophageal cancer, total thoracic esophagectomy with cervical esophagogastronomy and radical 2FLD associated with jejunostomy feeding tube placement should be performed.

For patients with esophagogastric junction cancer, total esophagectomy with cervical esophagogastrostomy and partial or extended gastrectomy, depending on the extensiveness of the gastric involvement, could be performed.

### 14.8.1.3 Neoadjuvant and Adjuvant Chemotherapy

The advantages of neoadjuvant chemotherapy are the downstaging of the tumor, facilitating surgery, as well as attacking micrometastases. But the risks could be significant toxicity, possible disease progression and the delay of curative surgical treatment. The benefit of neoadjuvant chemotherapy in comparison with surgery alone has been demonstrated in 5 trials and 2 meta-analyses [66–72].

Several studies did not show any survival benefit for neoadjuvant chemoradiotherapy comparing to chemotherapy alone [73, 74], but the preferred option in patients with esophagus cancers particularly the adenocarcinoma remains the preoperative chemoradiotherapy given the higher rates of pCRs and secondary complete resections (R0).

The main used drugs in esophageal cancer were cisplatin and 5FU but recently, adding docetaxel to cisplatin, and 5FU (DCF) in patients with clinical stage III or T3 esophageal SCC has shown its efficacy when compared to CF [75–78] with significantly better overall response rate in the DCF arm but with higher hemato-toxicity.

Regarding adjuvant setting, for patients with esophageal cancer who did not receive a preoperative chemotherapy or chemoradiotherapy, adjuvant chemotherapy alone may be beneficial, despite the low evidence of a survival advantage from randomized trials comparing to surgery alone [79–81].

A Japanese randomized trial compared surgery alone with surgery followed by adjuvant chemotherapy based on 2 courses of cisplatin and 5FU (CF) in patients with esophageal SCC [82]. The primary endpoint which was the 5-year disease-free survival rate was significantly higher with chemotherapy but not significant for overall survival maybe due to short duration of adjuvant chemotherapy (2 cycles).

Another Japanese trial (JCOG9907) compared postoperative chemotherapy with CF versus preoperative chemotherapy for stage II or III SCC of the thoracic esophagus. It showed that preoperative chemotherapy lead to significantly higher OS (55 versus 43%,  $p = 0.04$ ) [83].

Overall, and following the National Cancer care Network (NCCN) guidelines, adjuvant therapy with chemotherapy alone or chemoradiotherapy is recommended for patients with resected T3 or T4 esophageal adenocarcinomas or node-positive disease in addition to selected patients with high risk T2 N0 adenocarcinomas including poor differentiation, perineural invasion or lymphovascular, or young age who did not receive neoadjuvant treatment. For resected SCC without neoadjuvant treatment, the adjuvant therapy is recommended only in case of positive margins [84].

Regarding adenocarcinoma of the EGJ and lower esophagus, they are usually combined in trials with gastric cancers due to their molecular similarities.



The MAGIC study with perioperative administration of platinum-based chemotherapy in addition to the results from French trial ACCORD established perioperative chemotherapy as a new standard treatment for localized adenocarcinoma of the esophagogastric junction and lower esophagus with statistically significant disease free and overall survivals advantage for the group of patients which received perioperative chemotherapy [85, 86]. Another phase III clinical trial (FLOT4-AIO) compared perioperative treatment based on FLOT regimen (docetaxel, oxaliplatin, leucovorin and 5-FU) with ECF/ECX (5-FU or capecitabine with epirubicin and cisplatin) in patients with resectable gastric or EGJ adenocarcinoma. The 3-years OS was significantly better in the FLOT arm (median OS: 50 vs 35 months; HR 0.77 [0.63–0.94];  $p = 0.012$ ; 3-years OS: 57% vs 48%), and different toxicity profiles [87]. Therefore, FLOT also became a new perioperative treatment in resectable gastric or EGJ adenocarcinoma.

#### 14.8.1.4 Neoadjuvant and Definitive Radiotherapy/Chemoradiation

Radiotherapy alone was a common treatment used for local control of esophageal cancer before the era of chemotherapy and multimodal treatment. It has known many advances in radiation techniques in order to improve the safety profile especially with the development of 3-dimensional conformal radiation therapy (3D-CRT), and intensity-modulated radiation therapy (IMRT).

Around 32% of esophageal cancer patients have loco-regional disease at the moment of diagnosis, with modest rates of 5-year survival estimated at 10–30% [88]. With locally advanced disease (T3-4aN0, T1-4aN1M0), there are many treatment options available, with a major role of radiotherapy in a multimodal approach by combination of esophagectomy and chemoradiation or even definitive chemoradiation [89]. There is a survival benefit with chemo-radiotherapy vs radiotherapy alone as induction treatment for T3-4a tumors or node positive disease [90–92]. These findings were supported by CROSS trial that has shown a benefit in terms of survival with the induction chemoradiation using low-dose weekly carboplatin plus paclitaxel regimen as chemotherapy in combination with radiotherapy followed by surgical resection in comparison with surgery alone for patients with esophageal or esophagogastric junction cancer [93].

One of the most important trials was the RTOG 85-01 trial which compared RT alone (64 Gy) versus concurrent chemoradiotherapy with infusional FU plus cisplatin with RT 50 Gy (Herskovic regimen) in patients with locoregional thoracic esophageal cancer with 90% who had SCC. The results revealed a significant 5-years survival benefit in favor of chemoradiotherapy [94]. Therefore, definitive chemoradiotherapy became the standard of care for patients with unresectable disease and because of the high rate of local recurrences and persistent disease after chemoradiotherapy alone the addition of surgical resection is recommended. For patients who are nonresponders to chemoradiation or neoadjuvant chemotherapy, surgery must be considered when resectable disease is present [95].

Regarding cervical esophageal cancer, chemoradiation is the preferred option over surgery given the similar results in terms of survival with less morbidity.

### **14.8.2 Metastatic Disease**

Most of patients with esophageal cancer will need palliative treatment during the evolution of their disease, and around 50% of patients are metastatic at time of diagnosis [2].

Therapeutic options may include best supportive care, chemotherapy and enrollment in clinical trials if available. The main role of chemotherapy is to improve quality of life, provide symptom palliation, and prolong survival. Performance status, comorbidities, patient preference, symptom burden, and histologic type are crucial elements to choose the best therapeutic strategy.

#### **14.8.2.1 Chemotherapy**

- Adenocarcinoma:

The superiority of chemotherapy over supportive care was demonstrated in the meta-analysis of Wagner et al. [96].

The established standard for first-line therapy of irresectable or metastatic adenocarcinoma of the esophagogastric junction is a platinum analogue (cisplatin or oxaliplatin) in combination with a fluoropyrimidine [97].

In a phase III trial in gastric and gastroesophageal junction adenocarcinoma, the ECF (Epiribucin – cisplatin -5-FU) regimen showed its superiority in comparison with FAMTX regimen (5-FU, doxorubicin, and methotrexate) in terms of survival and with better safety profile [98].

Other trials have demonstrated the benefit of adding docetaxel in patients with metastatic gastroesophageal junction and showed superior response rate and time to tumor progression when compared to ECF [99]. The association of irinotecan and 5-FU in gastroesophageal junction cancers showed no difference with conventional 5-FU and cisplatin but with better safety profile in irinotecan arm [100].

- Squamous cell carcinoma:

The old chemotherapy protocol used in chemoradiation for locally advanced esophageal cancer including cisplatin and 5-FU including was also applied to the metastatic setting by the EORTC in 1997 and still continues to be the gold standard form of treatment for metastatic SCC but with lower response which ranged from 35% to 40%.

Other drugs have been added to this standard in order to improve the results. The addition of mitomycin in untreated patients with unresectable or metastatic SCC has showed a 61% major response rate but with high oxicity requiring treatment delay

in 46% of patients [100]. The addition of doxorubicin alone or with etoposide to 5-FU and cisplatin in SCC failed to improve the results obtained with cisplatin-5FU alone [102, 103].

#### 14.8.2.2 Targeted Therapies

- Anti-Her2 therapies:

For patients with adenocarcinoma of the EGJ, HER2 should be assessed before starting chemotherapy. The ToGA trial has compared trastuzumab in combination with cisplatin and 5-FU or capecitabine in advanced HER2-positive EGJ and gastric adenocarcinoma (as defined by 3 + immunohistochemical staining or fluorescence in situ hybridization positivity) to CF alone and has demonstrated a significantly better survival with trastuzumab (median 13.8 vs. 11.1 months) [104].

- Anti-angiogenic therapies:

Ramucirumab has shown its efficacy in second line treatment of metastatic EGJ and gastric adenocarcinoma after platinum- and fluoropyrimidine-containing chemotherapy as first-line. In REGARD trial, ramucirumab monotherapy significantly improved the OS compared to best supportive care (mOS of 5.2 vs 3.8 months; HR 0.776, 95% CI 0.603–0.998) [105]. In the RAINBOW trial, Ramucirumab in combination with paclitaxel has significantly increased the OS vs paclitaxel alone group (9.6 vs. 7.4 months; hazard ratio 0.81;  $p = 0.017$ ) [106].

Following these results, ramucirumab is a standard of care in second line treatment alone or combined to paclitaxel.

#### 14.8.2.3 Immune Checkpoint Inhibitors

Based on results from the phase II KEYNOTE-059 study, Pembrolizumab has shown an overall response rate (ORR) of 13.3% (95% CI, 8.2–20.0), including a complete response (CR) rate of 1.4% and a partial response (PR) rate of 11.9% in PD-L1-positive recurrent or advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received 2 or more lines of chemotherapy. Following these results, Pembrolizumab has been approved recently in this setting [107].

Additionally, The FDA has approved Pembrolizumab on unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, regardless of tumor histology [108].

### 14.8.2.4 Best Supportive Care

Best supportive care is often the most appropriate treatment option and patients' performance status should determine if chemotherapy may be added. Specific symptoms that often need palliation include dysphagia, pain, nausea, bleeding and obstruction. Feeding tubes may be reasonable options in some selected patients while radiotherapy or endoscopic treatments such as dilation and stenting may be used to palliate dysphagia or bleeding from esophageal cancer. Palliative esophagectomy for patients with metastatic disease may have a role in very few selected cases, because of the high burden of morbidity compared to the poor prognosis with or without surgery in such advanced stage [61–65].

## 14.9 Future Directions

### 14.9.1 Targeted Therapies

The epidermal growth factor receptor EGFR and the human epidermal growth factor receptor 2 (HER2) have an important role in the carcinogenesis of esophageal [32].

Two anti-EGFR monoclonal antibodies, nimotuzumab and cetuximab, have shown promising results in combination with chemotherapy among patients with SCC in both first-line and second-line treatment strategy [101, 109, 110].

An ongoing trial is assessing cetuximab in combination with chemoradiation in unresectable, locally advanced SCC and adenocarcinomas (NCT01787006). Another trial is also testing the role of nimotuzumab plus simultaneous integrated boost radiotherapy compared to paclitaxel and nedaplatin plus simultaneous integrated boost radiotherapy in a neoadjuvant settings for esophageal SCC (NCT02858206).

Regarding HER2 inhibition, a current study is investigating the combination of double blockade of HER2 by trastuzumab and pertuzumab with chemoradiation in neoadjuvant setting for Her2-overexpressed GEJ or esophageal adenocarcinomas (NCT02120911).

It is true that targeting the ErbB-family in esophageal carcinomas is not as effective as it is in other cancers, like breast and lung cancer but more trials and researches are strongly needed to identify the best strategy for their use.

### **14.9.2 Immunotherapy**

Several studies are currently ongoing to evaluate the role of many checkpoint inhibitors (anti-CTLA4 and anti-PD1/PDL1) alone or in combination with other therapies in different lines of treatment in patients with metastatic esophageal cancer.

The potential benefit of immune checkpoint inhibitors may be maximized if given early in the treatment course and concurrent with other therapies, such as chemotherapy and radiation therapy. An ongoing trial is evaluating this approach by testing pembrolizumab in combination with chemo-radiotherapy before surgery in patients with locally advanced gastroesophageal junction or Gastric Cardia Cancer That are potentially resectable (NCT02730546).

### **14.9.3 Vaccines**

A phase I trial has shown promising results with the use of an anti MAGE-A4 vaccine in 18 patients with advanced esophageal carcinoma. Of the 13 esophageal cancer patients that completed one cycle of vaccination, 3 patients responded and had a significant improvement in survival [111]. Other preliminary antiesophageal cancer vaccine trials reported success with an anti-NY-ESO1 vaccine and with a genetically engineered multi-epitope vaccine [112, 113].

The combination of dendritic cells (DCs) and cytokine-induced killer cells (CIKs) is currently under investigation in clinical trials in combination with radiation, chemotherapy and chemoradiotherapy for the treatment of esophageal cancer. (NCT01691664, NCT02644863, NCT01691625).

## **14.10 Conclusion**

Esophageal cancer is a heterogeneous disease characterized by various histological and molecular subtypes, different biologic pathways, and distinct sensitivities to chemotherapy and worse clinical outcomes. Treatment must be in a multidisciplinary approach and should be based on multimodal strategy including surgery, radiotherapy and chemotherapy. New targeted therapies and immunotherapeutic agents have shown promising results. The challenge is to conduct active research on more selected patients to discover additional specific targets and improve the outcome of patients with esophageal cancer.

**Key Points**

- Esophageal cancer (EC) is the eighth most common cancer worldwide, and the sixth most common cause of death related to cancer.
- The highest incident is reported in the region called “esophageal cancer belt” stretching from Northern Iran through the central Asian republics to North-Central China.
- The majority of EC is sporadic and the influence of hereditary factors remains uncertain.
- Risk factors known for Esophagus squamous cell carcinoma are tobacco, alcohol, N-nitroso components, high temperature beverages, red meat, low intake of fruits, vegetables and HPV.
- The major risk factors for esophageal adenocarcinoma are Barrett’s esophagus, gastroesophageal reflux disease, smoking, and a high body mass index.
- Esophageal SCC has a molecular profile similar with with head and neck SCC HPV negative, and esophagus adenocarcinoma is similar to chromosomal instability of gastric adenocarcinoma.
- Esophageal SCC showed frequent genomic amplifications of CCND1, SOX2 and/or TP63.
- Esophageal adenocarcinoma has frequent ERBB2, VEGFA, GATA4 and GATA6 genomic amplifications.
- Advanced esophagus cancer frequently presented with progressive dysphagia and weight loss.
- Diagnosis of esophageal cancer is usually established by endoscopic biopsy.
- Endoscopic ultrasound (EUS) is the preferred method for locoregional staging.
- Computed tomography of the neck, chest, and abdomen, with contrast is required to assess tumor extension to adjacent structures and distant metastases.
- Staging should be performed accordingly to the tumor, node, metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) for esophageal cancer.
- Treatment of esophagus cancer depends mainly on stage of the disease, tumor location, and patients’ medical conditions.
- Surgery is the backbone of treatment for localized disease.
- Adjuvant therapy (chemotherapy or chemoradiotherapy) is indicated for patients with T3-T4 or node-positive adenocarcinoma who did not receive neoadjuvant treatment.
- Adjuvant treatment for SCC is indicated only if positive margins.
- Perioperative chemotherapy is established as a standard treatment for localized adenocarcinoma of the lower esophagus and esophagogastric junction.
- Definitive chemoradiotherapy is a reasonable option for patients who are not candidates for surgery with consideration of resection for those who are still operable after chemotherapy.

- For cervical esophageal cancer, chemoradiotherapy is preferred over surgery.
- In the metastatic setting, best supportive care, palliative chemotherapy and enrolment in clinical trials are important options.
- Cisplatin and 5FU are the major drugs in metastatic setting.
- For adenocarcinoma of the EGJ, trastuzumab with chemotherapy is validated in first line in case of HER2 overexpression, and ramucirumab is approved in second line alone or with paclitaxel.
- Immunotherapy is very promising.

### Multiple Choice Questions

#### 1. Which answer is NOT correct about epidemiology of esophageal cancer?

- (a) The overall incidence is increasing
- (b) There is a clear female predominance
- (c) In western countries the incidence of adenocarcinoma is increasing
- (d) SCC is the most frequent histological type in black race
- (e) Adenocarcinoma is more frequent among white race

The overall incidence of esophageal cancer worldwide, is higher among men and this gender difference is even more marked in adenocarcinoma subtype.

#### 2. What is the geographic area with the higher incidence of esophageal cancer?

- (a) Western Europe
- (b) Central and Western Africa
- (c) Eastern Asia
- (d) North America
- (e) Latin America

Eastern Asia is included in the highest-risk area called the “esophageal cancer belt” which is stretching from Northern Iran through the central Asian republics to North-Central China.

#### 3. What are the most common histological subtypes of esophageal cancer?

- (a) Small cell carcinoma and lymphoma
- (b) Squamous cell carcinoma and adenocarcinoma
- (c) Sarcoma and neuroendocrine tumors
- (d) Melanoma and sarcoma
- (e) lymphoma and gastrointestinal stromal tumors

Squamous cell carcinoma and adenocarcinoma are the most frequent histological subtypes of esophageal cancer because esophagus is covered with epithelium. The squamous cell dysplasia can precede squamous cell carcinomas and dysplasia in Barrett’s esophagus can develop into adenocarcinoma.

#### 4. What is the most common risk factor for esophageal adenocarcinoma?

- (a) Gastroesophageal reflux disease and Barrett’s esophagus
- (b) Menopausis

- (c) Hepatitis B and C
- (d) Contraception
- (e) Low BMI

Barrett's esophagus represents as gastric or intestinal metaplasia can appear due to reflux of gastric fluid in the distal part of the esophagus. Dysplasia preferably appears in the intestinal metaplasia of Barrett's esophagus and can be a precursor lesion of esophageal adenocarcinoma.

**5. What is the most implicated risk factor for esophageal squamous cell carcinoma?**

- (a) Nulliparity
- (b) Smoking and alcohol consumption
- (c) Cold beverages and food
- (d) Low intake of meat
- (e) Sun exposition

Smoking and alcohol consumption are major risk factors for developing esophageal squamous carcinoma and also other aerodigestive cancers. Their role in the carcinogenesis by damaging the cellular DNA is confirmed after being extensively studied.

**6. What is the most implicated virus in esophageal squamous cell carcinoma?**

- (a) Hepatitis virus B
- (b) Hepatitis virus C
- (c) Epstein Barr virus
- (d) Human papilloma virus
- (e) Cytomegalovirus

Human papilloma virus has been implicated in the pathogenesis of esophageal squamous cell carcinoma particularly serotypes 16 and 18. Several meta-analyses have shown the association between HPV especially HPV-16 and esophageal SCC.

**7. What is the dietary factor most linked to esophageal cancer?**

- (a) High intake of fruit and vegetables
- (b) Sugar
- (c) Food containing Nitroso-components
- (d) Milk
- (e) Spicy food

Foods containing N-nitroso compounds have been identified as carcinogens that may exert their mutagenic potential by inducing alkyl adducts in DNA.

**8. What is the most frequent symptom of esophageal cancer?**

- (a) Disuria
- (b) Dysphagia



- (c) Back pain
- (d) Cough
- (e) Diarrhea

The obstruction of the esophagus by the tumor causes progressive dysphagia, and it usually occurs when the esophageal lumen diameter is less than 13 mm.

**9. What is the preferred exam for the locoregional evaluation of T stage and regional lymph node (N) in esophageal cancer?**

- (a) Abdominal ultrasound
- (b) PET scan
- (c) Endoscopic ultrasound (EUS)
- (d) Laparoscopy
- (e) Physical examination

EUS is the most accurate technique for locoregional staging of invasive esophageal cancer by using a high-frequency ultrasound transducer that provides detailed images of esophageal masses and their relationship with the five-layered structure of the esophageal wall. It also achieves nodal staging by imaging characteristics and by enabling FNA biopsy.

**10. Which exam is mandatory to appreciate the distant extension of esophageal cancer in first intention?**

- (a) Contrast-enhanced CT
- (b) Bone scan
- (c) Brain MRI
- (d) Pelvic ultrasound
- (e) Pelvic MRI

CT with contrast of the neck, chest and abdomen provides useful information, in a first intention, to detect distant metastases. PET/CT is carried out with intravenous contrast, and this might effectively replace the need for a separate contrast-enhanced CT, but this practice is not widespread.

**11. For metastatic esophagogastric junction adenocarcinoma, which molecular alteration should be assessed that may be targeted in first line?**

- (a) EGFR mutation
- (b) Her2
- (c) RAS
- (d) BRAF
- (e) ALK-EML4

Initial studies reported an over-expression of Her2 in 24% to 32% of esophageal and esogastric adenocarcinomas. Therefore, the assessment for HER2 status should be performed because anti-HER2 monoclonal antibody-targeted therapy, in combination with chemotherapy, has been shown to improve medial overall survival of patients with Her2 positive gastric and esogastric adenocarcinoma.

**12. For T1 N0 esophageal cancer, what is the recommended therapeutic option in first intention?**

- (a) Targeted therapy
- (b) Immunotherapy
- (c) Definitive radiotherapy
- (d) Chemotherapy
- (e) Surgery

Initial resection, rather than trimodality treatment, is recommended as initial therapeutic approach for patients with T1N0M0 esophageal cancer.

This recommendation is consistent with consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO).

**13. Adjuvant treatment (chemotherapy+/- radiotherapy) is recommended for esophageal adenocarcinoma with:**

- (a) T1 N0 disease
- (b) Tis disease
- (c) T3-T4 or N+ disease who did not receive neoadjuvant treatment.
- (d) Resected adenocarcinoma after neoadjuvant chemoradiation
- (e) T2N0 well differentiated, clear margin, without lymphovascular or perineural invasion

For patients with completely resected, node-positive or nodenegative, pathologic T3 or T4 esophageal adenocarcinomas who have not received neoadjuvant treatment, and also for high-risk pathologic T2N0 adenocarcinomas, postoperative therapy is suggested in an attempt to improve outcomes in keeping with National Comprehensive Cancer Network (NCCN) guidelines.

**14. In the perioperative setting for resectable adenocarcinoma of the lower esophagus and esophagogastric junction, the benefit of chemotherapy by ECF compared to surgery alone was in terms of:**

- (a) Disease free survival (DFS)
- (b) Overall survival (OS)
- (c) Safety profile
- (d) a + b.
- (e) pCR

The MAGIC trial has shown that In patients with operable gastric or lower esophageal adenocarcinomas, a perioperative regimen of ECF significantly improved progression-free and overall survival.

**15. What is the most appropriate strategy for locally advanced unresectable esophageal cancer?**

- (a) Chemoradiotherapy +/- surgery if resectable
- (b) Definitive radiotherapy
- (c) Radiotherapy followed by surgery
- (d) Palliative chemotherapy
- (e) Anti-PDL1

Several trials and meta-analyses have shown better survival with preoperative concurrent chemoradiation as compared with local therapy alone, and this approach is generally preferred for potentially resectable stage T3 or 4, or node-positive localized cancer of the thoracic esophagus regardless of histology.

**16. Which chemotherapy is recommended in concomittence with radiotherapy for SCC?**

- (a) Docetaxel
- (b) Mitomycin-5FU
- (c) Irinotecan
- (d) Cisplatin-5FU
- (e) Oxaliplatin

The RTOG 85-01 trial compared RT alone (64 Gy) versus concurrent chemoradiotherapy with infusional FU plus cisplatin and RT [50 Gy] in patients with locoregional thoracic esophageal cancer (90% of patients had SCC). The trial showed a significant 5 year-survival advantage for chemoradiotherapy.

**17. What is the most appropriate therapeutic option for metastatic esophageal cancer patient with ECOG PS 4?**

- (a) Cisplatin-5FU
- (b) Irinotecan-5FU
- (c) Carboplatin-paclitaxel
- (d) Docetaxel
- (e) Best supportive care

For patients with a poor performance status, poorly controlled comorbidity, or a preference for no additional therapy, supportive care alone is recommended to help improving quality of life.

**18. What is the possible option for patients with metastatic cancer of the esophagogastric junction who have received 2 or more lines of chemotherapy?**

- (a) Bevacizumab
- (b) Pembrolizumab
- (c) Cetuximab
- (d) Trastuzumab
- (e) Ipilimumab

In the phase II KEYNOTE-059 trial, Pembrolizumab has demonstrated an overall response rate (ORR) of 13.3% (95% CI, 8.2–20.0) in PD-L1–positive recurrent or advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received 2 or more lines of chemotherapy. Following these results, Pembrolizumab has been approved recently in this setting.

**Answers** 1-b; 2-c; 3-b; 4-a; 5-b; 6-d; 7-c; 8-b; 9-c; 10-a; 11-b; 12-e; 13-c; 14-d; 15-a; 16-d; 17-e; 18-b.

### Clinical Case

We report the case of a 57 years old man, with a past medical history marked by active smoking and alcohol consumption for 30 years. No personal or familial disease was reported. He was admitted for dysphagia progressively worsening from solids to liquids, immediate postprandial vomiting and weight loss of 6 kg over 3 months. Physical examination found a dehydrated patient, with performance's status 1, BMI at 22, and the rest of examination did not show any abnormality. Blood tests were unremarkable apart from iron deficiency anemia (hemoglobin 10 g/dl) and hypoalbuminaemia (albumin: 30 g/L, normal 39–50 g/L). An upper gastro-intestinal endoscopy was performed and found a 6 cm long mass in mid thoracic esophagus occupying more than 50% of circumference and multiples biopsies were performed with placement of nasogastric tube for feeding because of the progressive dysphagia. The histopathological examination of the endoscopic specimen revealed a well differentiated carcinoma expressing the p63 and therefore concluded to the diagnosis of squamous cell carcinoma. A thoracoabdominal scan showed a circumferential hypertrophy of the wall of the middle third of esophagus with direct invasion of the thoracic aorta in addition to a regional lymph node invasion but without distant metastases. Therefore the tumor was staged cT4N1M0.

Pet/CT confirmed the stage of locally advanced disease without distant metastases. Then the case was discussed in the multidisciplinary meeting and the tumor was staged as unresectable. The decision was to suggest radio-chemotherapy in order to obtain high objective response and then re-discuss the case after completing treatment to evaluate the response. The treatment option was discussed with the patient and after his consent; he received radiotherapy at the dose of 50Gy combined to chemotherapy based on infusional FU and cisplatin with tolerance that was marked by asthenia, anorexia, dryness and darkening of the skin in addition to grade II nausea and diarrhea. The patient received in parallel adequate treatments to manage chemo-radiation's side effects, in addition to adapted pain killers and regular follow-up by nutritionist and psychologist.

Six weeks after finishing his treatment, the dysphagia mostly resolved and the PET/CT showed a response estimated at 70%. Surgery was suggested due to persistent disease and the patient underwent a total esophagectomy with lymphadenectomy. Final histological analysis revealed a squamous cell carcinoma, invading the submucosa and no invasion on lymph nodes, ypT1N0. Postoperative recovery was uneventful and patient is still in good control after a follow-up of 18 months.

### Case Questions/Answers

Q1 – What are the risk factors of esophageal cancer in this case?

A1 – Smoking and alcohol are major risk factors for esophageal SCC and may have a synergistic effect on increasing the relative risk.

Q2 – What is the stage of the esophageal cancer in this case? And what is the appropriate therapeutic strategy?

A2 – T4N1M0 corresponds to stage IIIc, and the adequate strategy should include combined treatment with concurrent chemoradiotherapy +/- surgery.

Q3 – What is the scheme of chemo-radiotherapy that can be suggested in this case of stage IIIc SCC?

A3 – Two cycles of infusional FU [1000 mg/m per day, days 1–4, weeks 1 and 5] plus cisplatin [75 mg/m day 1 of weeks 1 and 5] and RT [50 Gy in 25 fractions over 5 weeks]) then two additional chemotherapy courses, 3 weeks apart, after RT based on the RTOG 85-01 trial.

Q4 – Is there a necessity to undergo surgery after chemoradiotherapy?

A4 – At least two randomized trials have directly compared chemoradiotherapy alone with chemoradiotherapy followed by surgery in patients with exclusively or predominantly with SCC. They showed no better survival with trimodality treatment. However, they both showed better locoregional control and a lesser need for palliative procedures when surgery is performed.

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# Chapter 15

## Gastric Cancer



**Luis Castelo-Branco, Karima Oualla, Pedro Castelo-Branco,  
and Ramon Andrade De Mello**

**Abstract** Gastric cancer (GC) is the third leading cause of cancer-related death in both sexes worldwide. It has a very heterogeneous distribution across the world, being more frequent in Eastern Asia and South Europe. *Helicobacter Pylori*, nitrosamine components, tobacco, previous radiation exposure, previous gastric surgery, preserved/salty food, are some of the well-known risk factors associated with this disease. Diagnosis is common during advanced stage of the disease, except on higher incidence regions where screening programs are already established. Progressive epigastric pain, asthenia, weight loss in addition to metastases related symptoms may reveal advanced disease. Upper gastrointestinal endoscopy, endoscopic ultrasonography and thoraco-abdomino-pelvic scan are required exams for appropriate diagnosis and staging. Around 90% are sporadic adenocarcinomas including intestinal or diffuse types from Lauren classification. Local ablations for early stages, surgery with lymphadenectomy, chemo-radiation or chemotherapy with different combinations of drugs are valid options, depending on the disease stage and patient

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individual conditions. More recently, novel targeted therapies including trastuzumab and ramucirumab in addition to immune checkpoint inhibitors were approved in metastatic setting. Due to recent research and increased molecular and genetic knowledge, the near future might bring more valuable treatments, including different combinations, to better help those who suffer from gastric cancer.

**Keywords** Gastric cancer · Adenocarcinoma · Clinical staging · Treatment modalities · Chemotherapy

## Abbreviations

ACRG	Asian Cancer Research Group
CT	Computed tomography
EUS	Endoscopic ultrasonography
GC	Gastric cancer
GERD	Gastro Esophageal Reflux Disease
ICI	Immune Checkpoint Inhibitors
OS	Overall Survival
TCGA	The Cancer Genome Atlas

## 15.1 Introduction

Gastric cancer is a highly aggressive and lethal disease that continues to impact heavily the global health. It remains one of the most common forms of cancer worldwide and a leading cause of cancer-related death. It is a heterogenous disease with significant geographical, ethnic, and socioeconomic differences in distribution (1,2).

Surgery remains the only curative therapy, while perioperative and adjuvant chemotherapy, as well as chemoradiation, improve outcome of resectable gastric cancer. However, more than 50% of patients radically resected for gastric cancer relapse locally or with distant metastases, or have metastatic disease at the time of diagnosis leading to poor survival. Despite significant advances in surgery, radiotherapy and chemotherapy, in addition to the development of novel therapeutic agents, survival has shown only minor improvement, but the increased knowledge on biomolecular alterations and signaling pathways is allowing the development of novel targeted therapies for gastric cancer.

## 15.2 Epidemiology

- Gastric cancer (GC) is the third leading cause of cancer-related death in both sexes worldwide;

- GC has a higher incidence in Eastern Asia and South Europe and lower in western world;
- 90% cases are sporadic and only 10% had a familial component;
- Helicobacter Pylori, nitrosamine components, tobacco, previous radiation, previous gastric surgery, preserved/salty food, are some of the well-known risk factors.

### 15.2.1 Incidence and Prevalence

Gastric Cancer (GC) is a very heterogeneous disease, with high prevalence in some geographic areas and significant epidemiologic changes over the last decades. In fact, the world prevalence of GC changed from the leading cause of cancer in 1975 to the fifth most common cancer in the world, with 952,000 cases diagnosed in 2012 [16]. It is also the third leading cause of cancer-related death in both sexes worldwide. The worldwide incidence of gastric cancer has been on the decline over the last few decades. This decline may be partially explained by the recognition of certain risk factors especially environmental risks and *H. pylori*. This decline was seen first in countries with low incidence, while the decline was slower in high incidence countries such as Japan. But despite global epidemiological changes, there are some geographic particularities: the highest rates are reported in Eastern Asia, Eastern Europe, and South America, while the lowest rates are in North America, Northern Europe, and most countries in Africa and South Eastern Asia. More than 70% of cases of GC occur in developing countries and 50% occurs in Eastern Asia, and it is more frequent in men than in women, in both developed and developing countries [16]. Some other geographic areas have high incidence including Southern Europe, particularly Portugal, where this disease is the sixth most common malignancy, and an important public health concern [49]. However, in other parts of the Western world like North America, this is one of the least common cancers. In 2017, GC represented 1.7% of all cancer cases in the USA (with 28,000 new cases/year), with 5-year relative survival rates of 67.2% for localized disease, 30.7% for regional disease and 5.2% for distant disease (<https://seer.cancer.gov/statfacts/html/stomach.html>). There is a substantial difference in the incidence within the same region. A difference in incidence and mortality from north to south was observed in several countries like Japan where gastric cancer mortality and incidence are higher in the northeastern regions. Rates also differ across races like in United states where rates are higher in Latinos than in non-Hispanic White populations.

GC is more frequent in low socioeconomic regions probably due to a conjugation of factors, such as higher incidence of *H. Pylori*, higher intake of salty food and lower intake of fresh fruits and vegetables [30]. Globally around 50% of GC patients are diagnosed with advanced stage disease, but in endemic countries such as Japan or Korea where the screening is recommended, early detection is more frequent. There has been a steady decrease in global gastric cancer mortality, with a variation by regions. An annual percent change (APC) in mortality rate of  $-3\%$  to  $-4\%$  was

reported for the main European countries. This APC rates were similar for Korea, Japan and the United States, while it was less important In Latin America. The 5-year overall survival of metastatic GC might range from 3 months with only supportive care treatment to 16 months with active systemic treatment thus, GC treatment is still an unmet need in oncology.

### 15.2.2 Risk Factors

As with many other cancers, genetic and environmental exposition have a role in GC development. But the fact that second and third generations of Japanese descendants living in USA decreased their GC rates, comparing with their first generation relatives, suggests that environmental factors might have a strong role in GC development [39]. Few studies have been conducted in low-income countries with high GC incidence, and more research on such countries could contribute to a better understanding of this disease.

There are some well-known risk factors associated with GC, such as *Helicobacter pylori* advanced age, male sex, smoking, hereditary factors or previous radiation exposure [30]. Obesity and Gastro Esophageal Reflux Disease (GERD) are also risk factors for cardia (proximal) gastric cancer. Also, low socioeconomic status, high intake of salty and smoked foods and low consumption of fruits and vegetables are associated with non-cardia gastric cancer. [30]. Gastric reflux and Barrett's oesophagus increases the risk of gastroesophageal junction tumors, and are more common in non-Asian countries [13]. The median age at diagnosis of GC in USA is 70 years old [26], and it has a twofold greater incidence in men than in women [17].

*Helicobacter pylori* is present in around 90% of non-cardia gastric cancers [38] and is a major risk factor in GC, particularly on positive strains for cytotoxin-associated gene A (CagA) [53]. Chronic inflammation and its direct effect on epithelial gastric cells is likely to play a major role in such oncogenic process. [5]. Nowadays, there is evidence that *helicobacter pylori* eradication decreases incidence and death from GC [59] [18], thus this might be a relevant public health strategy, particularly on high incidence areas.

Tobacco increases the risk of GC, in both sexes, in cardia and non-cardia cancers, and this risk seems to be lower in former or light smokers [31]. Higher intake of salt also increases the risk of GC by 22% [22], but the exact mechanism by which this happens is still unknown. A systematic review from 1985 to 2005 found a positive association between preserved or processed food (meat, fish or even vegetables), smoked food, nitrites and nitrosamines intake and GC. [23]. More recently, a meta-analysis published in 2015 concluded that increased consumption of nitrites and nitrosamines seemed to be risk factors for GC [57], but more studies are needed to clarify this relationship. Regarding obesity, higher body mass index has more evident association with cardia-gastric cancer incidence, than with non-cardia gastric cancer. [4]. Gastro-esophageal reflux disease (GERD) is a well-known risk factor in esophagus cancer, and there also evidence between GERD and cardia GC, but not with

non-cardia GC. [30]. Previous gastric surgery was found also as a risk factor for GC [17]. The pathologic pathway is not completely understood, but perhaps pH gastric changes after surgery might increase metaplastic and dysplastic changes. [42].

### 15.2.3 Genetic Risk Factors

Only 1–3% of GC is related to genetic predisposition and 5–10% might have a familial component [44, 13]. Hereditary diffuse gastric cancer, lynch syndrome, juvenile polyposis syndrome, peutz jehgers syndrome, Li–Fraumeni syndrome, and familial adenomatous polyposis are important syndromes related to GC [3]. If a genetic syndrome is suspected based on clinical and/or familial history, a genetic counseling should be considered.

## 15.3 Molecular Classification

- TCGA divided gastric adenocarcinomas into four genetically defined molecular subtypes: Chromosomally instability, microsatellite-unstable, genomically stable and tumors positive for Epstein–Barr virus;
- EBV subtype has better prognosis, followed by microsatellite-unstable, chromosomal instability, while genomically stable subtype has the worst prognosis;
- The Asian Cancer Research Group (ACRG) proposed another classification based on gene expression: microsatellite-unstable type, mesenchymal-like type, p53-active or p53-inactive types.

There are different classifications for GC, and the recent advances on molecular and genomic knowledge were important to sub-classify this disease.

The Cancer Genome Atlas (TCGA) molecularly evaluated 295 primary gastric adenocarcinomas and suggested the division of gastric adenocarcinomas into four genetically defined molecular subtypes: Chromosomally unstable (50%), microsatellite unstable (22%), genomically stable and positive tumors for Epstein–Barr virus (9%).

Chromosomally unstable tumors have particular gene amplifications, such as HER2, EGFR, MET, CCNE1, CCND1, CDK6, VEGFA and FGFR2. The microsatellite unstable tumors are characterized by elevated mutation/hypermethylation rates, a median age of 72 years and a higher (56%) female gender rate. On the Genomically stable subtype, major genetic alterations are RHOA signaling mutations, CLDN18–ARHGAP26 fusion, in addition to FGFR2 and VEGFA amplification. The Epstein Barr Virus subtype is more common in fundus or body cancers, in males (81%), has high levels of DNA promoter hypermethylation, elevated expression of PD-L1 and PD-L2, JAK2 amplification and PIK3CA mutation.

Following the TCGA classification, the EBV subtype was associated with best prognosis, followed by microsatellite-unstable and chromosomally unstable subtypes, while genomically stable subtype was associated with the worst prognosis.

More recently, The Asian Cancer Research Group (ACRG) proposed another classification based on gene expression comprising four subtypes: a microsatellite-unstable type, mesenchymal-like type, and p53-active or p53-inactive types. Microsatellite-unstable subtype has the best prognosis and the mesenchymal-like type is associated with the worse prognosis.

Indeed, the identification of these subtypes (based on TCGA or ACRG classification) might be useful for clinical decisions, prognostic and development of new targeted therapies (see future developments section).

## 15.4 Diagnosis and Staging

- Frequent but unspecific symptoms related with GC are progressive epigastric pain, dysphagia, asthenia, loss of appetite or weight loss;
- Upper gastrointestinal endoscopy plays an essential role on the diagnosis of gastric lesions, including GC;
- Endoscopic ultrasonography is very useful for assessing small lesions (T1-T2) depth of invasion of primary GC and local lymph nodes;
- Computed tomography scan should be routinely used pre-operatively and is useful assessing T stage, lymph nodes and metastasis;
- Laparoscopy with peritoneal washings should be performed on potentially resectable GCs.

### 15.4.1 Clinical Evolution

Screening programs in high risk areas such as Japan and South Korea are helpful in diagnosing early stages of GC in asymptomatic patients. However the majority of cases arising on non-screening areas will be diagnosed following clinical symptoms. Early stage of the disease is often asymptomatic and the diagnosis is made frequently at an advanced stage [36]. An appropriate process of history taking, communication and physical examination, in a close confident and trustable relationship with patient, should be implemented in medicine [34], and that is particularly relevant with oncology diseases.

Progressive epigastric pain, indigestion, dysphagia, nausea and vomiting are common, but non-specific, symptoms that might be more intense with disease evolution. Other symptoms may be reported in advanced disease including asthenia, loss of appetite, early satiety, weight loss and even cancer cachexia. Melenas or hematemesis might appear in ulcerated or advanced stages, leading to anemia. GC spreads mainly to liver, peritoneal surface, via lymph nodes, to lungs, bone, brain or



ovaries [37]. But the patterns of metastasis changes with histology and cancer localization. A Swedish study on 7559 GC patients found that the most common sites of metastasis are liver (48%), peritoneum (32%), lung (15%), and bone (12%). [46]. Cardia cancer had more lung, nervous system, and bone metastases, and non-cardia cancer more frequently metastasized within the peritoneum. Signet ring has a particular spreading pathway, with more metastases within the peritoneum, bone and ovaries. Ascites can be present due to peritoneal carcinomatosis or hepatic failure, and jaundice and other hepatic failure symptoms are frequent with significant hepatic metastasis or extra-hepatic obstruction. Peritoneal spread on woman could originate also an enlarged ovary – Krukenberg’s tumor. Dyspnea is frequent with pleural effusion, due to pleural/lung metastasis or even when anasarca is present due to hepatic failure.

At physical examination, an enlarged epigastric mass and hepatomegaly could be found. The lymphatic spread of GC can lead to an isolated left supra-clavicular node (Virchow node) or left anterior axillar node (Irish node). In more advanced stages a peri-umbilical mass might be palpable (Sister Mary Joseph nodule). Several blood tests should be performed including a hemogram that assesses mainly the anemia, in addition to liver and kidney tests that are useful for potential dose adjustments.

### 15.4.2 *Diagnosis*

Like in many other cancers, different exams are useful in GC.

Upper gastrointestinal endoscopy plays an essential role the diagnosis of gastric lesions, including GC [14]. Around 25% GC have the presence of gastric ulcer [37], and in the presence of ulcerated lesions, many biopsies should be performed in order to increase diagnosis accuracy. Brush cytology could be a complementary exam when multi-biopsies cannot be performed, such as in the context of bleeding lesions. Barium studies have a high rate of false negatives, and thus a limited role in diagnosing GC. But it might be complementary of endoscopy in some cases, such as diffuse GC, particularly with linitis plastica.

Endoscopic ultrasonography (EUS) should be performed regularly on non-metastatic gastric cancers [40]. This technique is very useful for assessing small lesions (T1-T2) depth of invasion of primary GC and local lymph nodes, but distant nodal assessment and T3-T4 lesions benefit from CT complementary image. EUS might be also important to guide fine needle aspiration of suspicious nodes.

Computed tomography (CT) scan should be routinely used before surgery. Abdominal CT scan accurately assesses the T stage of the primary tumor on around 50 to 70 percent of cases, and sensitivity for regional nodal metastases range from 65 to 97% [37, 13, 47]. Malignant lymph nodes on CT are normally round shaped, might have central necrosis and high enhancement [13]. CT is useful to diagnose visceral metastasis or ascites, but has low accuracy on peritoneal metastasis. Since chest x-ray has low accuracy diagnosing small metastasis, a chest CT is recommended for staging.

The role of PET is controversial. PET alone has low diagnostic rate but PET/CT FDG significantly increased lesions detection [40]. Some tumors also have low FDG avidity (such as diffuse type cancers or those with low metabolic rate), which might lead to false negatives using this technique [13]. PET/CT is also an expensive exam and of difficult accessibility in some geographic areas. Thus, the time to access and cost/benefit should be taken into account on the decision to proceed with this exam. Generally, when CT scan is not conclusive, PET/CT FDG could be considered to add information for a better clinical decision.

Peritoneal dissemination is common on GC, and in different series, around 25% of patients with  $T \geq 2$  stage on EUS have peritoneal metastases not detected on CT scan [37]. Thus, NCCN guidelines recommend staging laparoscopy and peritoneal cytology routinely with  $T \geq 2$ , without previous evidence of distant metastasis [40]. ESMO guidelines also recommend laparoscopy with peritoneal washings for all potentially resectable stage IB–III GC. [13].

The role of tumor markers in GC is still unclear. Carcinoembryonic antigen (CEA), glycoprotein, carbohydrate antigen 19-9 (CA 19-9), cancer antigen 72-4 (CA 72-4) or even  $\beta$ -subunit of human chorionic gonadotropin (hCG $\beta$ ) may be elevated in GC [6, 52]. Their utility is low on early GC, but those tumor markers may play an important role peri-surgery, detecting recurrence or predicting patient survival [52]. Tumor markers should be complementary to clinical and imaging assessment.

A very rare (0,17% to 0,78% of GC) and very aggressive subgroup of GC produce high levels of alpha-fetoprotein (AFP) – the so-called hepatoid adenocarcinomas of the stomach [58]. On such cases, AFP could be tested for disease follow up.

### 15.4.3 Staging

The TNM (tumor, node, and metastasis) staging system developed jointly by American Joint Committee on Cancer (AJCC) and Union for International cancer control (UICC) is widely used across world (Table 15.1). Tumors with epicenter up to 2 cm into the proximal stomach are staged as esophageal cancers and those with epicenter beyond 2 cm of proximal stomach are staged as GC. Regarding lymph node invasion, distant involvement including pancreatoduodenal, peripancreatic, retropancreatic, retroperitoneal, superior mesenteric, middle colic, paraaortic, are considered distant metastases. During surgery, a minimum of 15 examined lymph nodes should be assessed for adequate staging [40].

### 15.4.4 Pathology

Ninety per cent of gastric cancers are adenocarcinomas. Lauren classification first published on 1965 and still used today, divided it into two major histologic groups: Intestinal and diffuse GC adenocarcinomas [32]. The other 10% GC are commonly gastrointestinal stromal tumors (GISTs), lymphomas and neuroendocrine tumors. [13].

**Table 15.1** Stomach cancer TNM staging AJCC UICC 2017

Category	Criteria
<b>T Category</b>	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i> : Intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades the serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
<b>N Category</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
<b>M Category</b>	
M0	No distant metastasis
M1	Distant metastasis

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Intestinal GC has tubular or glandular formations and is associated with intestinal metaplasia and atrophic gastritis. Diffuse GCs present signet ring cells with high mucin content and loss of E-cadherin, which facilitates distant dissemination and present worse prognosis [44, 32]. Intestinal subtype is more frequent (54–74%) followed by diffuse subtype (16–32%) and others/mixed subtypes (10–15%). [64, 45].

World Health Organization (WHO) also divided GC adenocarcinomas in different groups, which include four major histologic patterns: tubular, papillary, mucinous and poorly cohesive, and finally uncommon histologies. [33]. Such classification should be routinely reported on the pathology assessment.

## 15.5 Treatment Approaches

- Treatment decision should be performed in a multidisciplinary team meeting;
- Small lesions with only submucosal invasion could be treated by only endoscopic mucosal resection or dissection;

- Other higher stage locoregional disease benefit from surgery with perioperative treatment;
- Different combinations of anthracyclines, platines, fluoropyrimidines and taxanes are valid chemotherapy options in GC;
- Trastuzumab (in HER2 overexpression tumors), ramucirumab and Pembrolizumab are approved in metastatic setting.

Treating GC is a worldwide challenge. Multidisciplinary treatment decision should be performed routinely [13], with the presence of medical oncologists, surgeons, radiotherapist, radiologist, pathologist, nurses, among others. Surgery, radiotherapy, classic chemotherapy and target therapies are currently treatment options, depending on the type and stage of GC.

## 15.5.1 *Locoregional Disease*

### 15.5.1.1 *Surgery*

Small lesions with only submucosal invasion (T1a), well differentiated,  $\leq 2$  cm and non-ulcerated could be cured just by endoscopic mucosal resection or dissection [37, 56]. However, radical gastrectomy with perioperative treatment is indicated in stages Ib to III, unless 5 cm (8 cm in diffuse tumors) to gastroesophageal junction could be preserved, which allows sub-total gastrectomy [13].

An important aspect of GC surgery is the type of lymph nodes dissection, which is still a controversial topic. The UICC/AJCC TNM (seventh edition) classification recommends excision of a minimum of 15 lymph nodes to allow reliable N staging.

Japanese guidelines recommend the extent of lymphadenectomy, classified as D0, D1, D1+ or D2, depending on the type of gastrectomy approach. [28]. From Japanese Gastric Cancer Association (JGCA) guidelines, for total gastrectomy, a D1 dissection includes lymph nodes stations from 1 to 7, D2 dissection includes D1 plus station 8a, 10, 11p, 11d, 12a, D0 is a lymphadenectomy inferior to D1, and D1+ adds station 8a, 9 and 11p [28].

Many international guidelines recommend D2 lymphadenectomy in advanced gastric cancer, with pancreas and spleen preservation, but the advantage of D2 dissection vs D1 is still controversial and different trials failed to show that benefit. An Italian randomized clinical trial assessed survival after D1 or D2 gastrectomy for gastric cancer, comparing 267 patients (1:1 randomization). Five-years survival was similar on both groups, but a population with advanced disease and lymph node metastases had better survival with D2 lymphadenectomy (59% vs 38%;  $P = 0.055$ ). [10]

Therefore the use of modified radical lymphadenectomy (D1+) instead of D2 can be an attractive option given its better safety and the similar results in terms of survival comparing to D2, as showed in some recent studies [11, 20].

Surgeries should be performed by experienced teams. A laparoscopy could lead to less post-operative morbidity, but high experience for the appropriate technique, including lymph node dissection is required. It is still unclear in which circumstances laparoscopy could be recommended, but perhaps more aggressive surgeries (such as D2 lymph nodes dissection) might benefit from laparotomy. For less aggressive surgeries, laparoscopy could be considered, but always depending on the center and team experience/results. The role of metastasectomy (liver or lung) [19] or hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer is still unclear.[15]

Before and after gastrectomy, an appropriate assessment on nutritional status is mandatory. Post prandial fullness is frequent after surgery, and individual food intake adaptation should be considered.

Deficiency in Vitamin B12 and iron, leading to anemia, are very frequent after gastrectomy [48]. Thus, oral or parenteral replacement should be considered. Other nutritional deficiencies such as vitamins or minerals are also frequent, and should be assessed regularly, and corrected.

### 15.5.1.2 Chemotherapy

An important question is the benefit of adding chemotherapy to surgery given the poor long-term outcomes with surgery alone. On MAGIC clinical trial, patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus were randomized to receive either surgery with perioperative chemotherapy (epirubicin cisplatin and fluorouracil-250 patients) or surgery alone (253 patients). The five-year survival on perioperative chemotherapy and surgery group was 36% vs 23% on surgery only group (hazard ratio for death, 0.75; 95% confidence interval, 0.60–0.93;  $P = 0.009$ ) [7].

The FNCLCC and FFCD multicenter clinical trials, compared perioperative chemotherapy (cisplatin and fluorouracil) with surgery alone on resectable esophagus or gastric adenocarcinomas. Despite a relevant grade 3 and 4 toxicity (38%, mainly neutropenia), postoperative morbidity was similar on both groups and the 5 year OS was favorable to the perioperative chemotherapy group (38% vs 24%; hazard ratio [HR] for death: 0.69; 95% CI, 0.50 to 0.95;  $P = .02$ ) [65].

After these positive results, different combinations of anthracyclines, platines and fluoropyrimidines were tested on advanced gastric cancer, such as using oral capecitabine instead of endovenous 5-FU, or oxaliplatin instead of cisplatin [13, 8].

More recently, the FLOT4-AIO phase III clinical trial compared FLOT (docetaxel, oxaliplatin, leucovorin and 5-FU) with ECF/ECX (5-FU or capecitabine as fluoropyrimidine) as a perioperative treatment on 716 (1:1) patients with resectable gastric or GEJ adenocarcinoma. The median and 3 years OS was favorable to the FLOT group (median OS: 50 vs 35 months; HR 0.77 [0.63–0.94];  $p = 0.012$ ; 3 years OS: 57% vs 48%), and the toxicity profile was different, with more neutropenia on FLOT group vs nausea and vomiting on ECF/ECX patients. [51]. Thus, FLOT became also a new standard in this setting.

On patients who did not performed neo-adjuvant (pre-operative) chemotherapy, two Asiatic clinical trials (ACTS and CLASSIC) demonstrated benefit of adjuvant chemotherapy after curative D2 lymph node dissection. [50] [2, 40]. A large meta-analysis from the GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, which included 17 trials, demonstrated that adjuvant chemotherapy based on fluorouracil regimens was associated with reduced risk of death compared with surgery alone (5 years OS: 55,3% vs 49,6%) [21].

ESMO guidelines recommend perioperative (pre- and postoperative 2–3 months) chemotherapy with a platinum/fluoropyrimidine combination on  $\geq$ Stage IB resectable GC, and postoperative chemoradiotherapy or adjuvant chemotherapy to those who did not performed preoperative chemotherapy [13].

### 15.5.1.3 Radiotherapy

NCCN guidelines recognize the role of Radiotherapy (RT) (preoperative, postoperative or palliative) on GC [40]. Radiotherapy in GC should target gastric bed, anastomoses and the draining regional lymph nodes.

A systematic review and meta-analysis showed a statistically significant 5-year survival benefit with the addition of radiotherapy in patients with resectable gastric cancer. [61].

The phase 3 clinical trial INT-0116 demonstrates strong and persistent benefit of adjuvant radiochemotherapy on  $\geq$  T3 and/or node-positive gastric cancer after R0 resection [55].

RT alone did not shown benefit on advanced GC [25] but adjuvant chemoradiotherapy might play a therapeutic role on this disease [13].

On a randomized clinical trial, RT (45 Gy in 25 fractions) with 5-FU improved OS comparing with surgery alone (3-year OS: 50% vs 41%) [35]. The update of this trial after a median follow-up of 10 years confirmed this benefit in survival, but also showed that there is no benefit among women and among patients with signet ring cell subtype. [55]. However, chemoradiotherapy might not provide benefit in patients who underwent an extensive D2 lymphadenectomy [12].

## 15.5.2 Metastatic Disease

Chemotherapy regimens, including different combinations of platinum, fluoropyrimidine, taxanes and anthracyclines, are a classic backbone in the treatment of advanced GC. Targeted therapy and immune checkpoint inhibitors have been incorporated in this framework more recently.

The REAL 2 phase III clinical trial demonstrate that capecitabine and oxaliplatin are at least as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer. [8]. More recently, a meta-analysis from REAL-2 and ML17032 trials confirmed benefit from the addition of an anthra-

cycline to a platinum and fluoropyrimidine doublet in GC. [43]. Other trials also shown that the inclusion of docetaxel or irinotecan (FOLFIRI) is a valid option to treat advanced GC [9, 24, 63].

In conclusion, different combinations of chemotherapy are valid therapeutic options for metastatic GC. Patient condition, comorbidities and different toxicity profiles could be integrated on mutual decision with patient.

HER2 overexpression in gastric cancer ranges from 9 to 23% and is more frequent in the intestinal subtype. Its prognostic value in GC remains unclear, but HER2 should be tested in all GC metastatic patients, by an IHC-modified scoring system.

In the ToGA trial, there was a median overall survival of 13.8 months in those assigned to trastuzumab plus fluoropyrimidine and cisplatin versus 11.1 months in the chemotherapy alone group, which led to the FDA approval of trastuzumab in combination with chemotherapy as a new standard first line treatment for patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer in 2010.

The high relevance of new blood vessels for cancer growth and survival is well known and over-expression of angiogenic markers is associated with more aggressive GC disease.

Ramucirumab, a human monoclonal antibody against VEGFR-2, demonstrated benefit in the second-line treatment of advanced GC following the REGARD and RAINBOW phase III clinical trials. In the REGARD trial, there was a median OS of 5,2 months (IQR 2.3–9.9) in the ramucirumab group and 3,8 months (1.7–7.1) in placebo group (HR 0.776, 95% CI 0.603–0.998). In the RAINBOW trial, OS was longer in the ramucirumab plus paclitaxel group vs paclitaxel alone group (median, 9.6 months [95% CI 8.5–10.8] vs 7.4 months [95% CI 6.3–8.4]; hazard ratio, 0.807 [95% CI 0.678–0.962]).

Apatinib, another drug targeting VEGFR-2, following phase II and III clinical trials, demonstrated statistically significant benefit in patients with chemotherapy-refractory advanced or metastatic GC, becoming a possible third- or further-line treatment. Those clinical trials enrolled Asiatic population only, thus it is still unclear its meaning among non-Asiatic population.

There are some concerns regarding the cost/effectiveness of ramucirumab and apatinib in GC. There is a marginal benefit of apatinib (1.8 months) and ramucirumab (1.4–2.2 months), but hopefully, further research on biomarkers, combination therapies, sequencing or maintenance therapies may bring more significant results for targeting VEGF in GC.

New immune-oncology modalities such as immune checkpoint inhibitors are playing a rapid important role across different tumors, including in GC.

The presence of high somatic mutations, PDL1 expression, MSI-H and mismatch repair deficiency raises a rationale for the use of immune checkpoint inhibitors in GC. Some anti-PD1 drugs demonstrated already encouraging results in this setting [40].

In May 2017, FDA approved Pembrolizumab on unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid

tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, regardless of tumor histology. [60].

Early phases I and II clinical trials led to FDA accelerated approval of Pembrolizumab in patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma. However, in phase III trial, KEYNOTE-061, pembrolizumab did not meet its primary endpoint of overall survival HR 0.82, (95% CI 0.66–1.03  $p = 0.042$ ) as second line treatment in patients whose tumor expressed PDL1 > 1%. It is possible that PDL-1 is not a good biomarker for anti pd1 drugs in GC or that limiting PDL-1 to 1% was too optimistic.

Nivolumab, on a phase III clinical trial that included heavily treated (at least 2 previous lines of chemotherapy) advanced gastric or GEJ tumors, showed a significant improvement in OS at 1 one year when compared to the placebo group (26.2%, 95% CI 20.7–32.0; vs 10.9%, 6.2–17.0).

More upcoming studies will be very helpful to determine the exact role of pembrolizumab, nivolumab or other immune checkpoint inhibitors in GC.

### 15.5.3 Follow-Up

There is low evidence on best strategies for gastric cancer follow-up, and as expected advanced stages of disease have a higher rate and earlier time to relapse [29]. Since around 90% of relapses will come on first 5 years [40], the NCCN recommendations for at least 5 years follow up seems an appropriate strategy.

Clinical (including nutritional assessment after surgery), CT-scan, hemogram and tumor biomarkers (CEA, Ca 19,9, CA 72,4) should be performed regularly during this period, and upper gastro-intestinal endoscopy should also be considered. During the first year, quarterly consultations are advised, and after that period it can be reduced to a six-month follow up. When there are doubts regarding disease recurrence, the follow up could be more regular and other exams, such as PET/CT may be added. Psychology and social support could be offered to all patients and relatives, depending on their needs and coping strategies.

## 15.6 Future Developments

- TCGA and the ACRG molecular classifications could contribute for future targeted therapies in GC;
- High plasma VEGF-A and low tumor neuropilin-1 were found as potential biomarker candidates for predicting clinical outcome in patients with advanced gastric cancer treated with bevacizumab;
- Trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate, showed tumor activity in patients with advanced gastric or gastro-esophageal tumors;



- EGFR overexpression may be a biomarker for anti-EGFR therapy in GC;
- Different conjugations with immune checkpoint inhibitors will probably increase the benefit of these drugs in GC.

An article published at ASCO educational book 2018 from De Mello, Castelo-Branco et al., precisely addressed the question of what might be expected from novel therapies in gastric cancer.

TCGA and the ACRG molecular classifications of gastric cancers could contribute in the identification of potential biomarkers that might help the development of new targeted therapies, the design of new clinical trials and retrospective sub-analysis of completed trials. HER2 amplification tumors, VEGF, EGFR, PIK3CA, PARP, and FGFR are promising pathways in such process. Also, high microsatellite instability (MSI-H), mismatch repair deficiency and high PD-L1/PD-L2 expression raises the potential for the immune-therapy in Gastric Cancer.

The already positive results with trastuzumab (in HER2 overexpressed GC), ramucirumab and Apatinib (anti-VEGFR) raised interest in more research targeting HER2 and angiogenesis respectively.

### **Angiogenesis**

It is still intriguing why ramucirumab and apatinib had positive results in GC and bevacizumab did not.

Despite Bevacizumab (anti-VEGF antibody) overall negative results on AVATAR and AVAGAST phase III clinical trials in advanced gastric cancer, on a further biomarker evaluation of AVAGAST trial, high plasma VEGF-A (HR, 0.72; 95% CI, 0.57 to 0.93) and low tumor neuropilin-1 (HR, 0.75; 95% CI, 0.59 to 0.97) were found as potential biomarker candidates for predicting clinical outcome in patients with advanced gastric cancer treated with bevacizumab [62]. More studies might contribute to redefine subpopulations that might benefit from drugs targeting angiogenesis, including bevacizumab.

### **Human Epidermal Growth Factor Receptor 2 (HER2)**

Unlike breast cancers, the results from targeting HER2 in advanced GC have not been consistently positive. The JACOB trial failed to demonstrate the benefit of trastuzumab and chemotherapy ± pertuzumab (double HER2 blockage) on first line HER2-positive metastatic or locally advanced unresectable gastro-oesophageal junction or gastric cancer. Also TRIO-013/LOGIC and TyTan trials failed to demonstrate the benefit of lapatinib in advanced GC. However, there are still many potential clinical benefits for different targeting combinations for HER2-positive disease with different combinations of monoclonal antibodies, such as trastuzumab, pertuzumab, TDM-1 or the tyrosine kinase inhibitor lapatinib combined with chemotherapy or radiotherapy. In 2017, a phase I study addressed the safety and tumor activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate, in patients with advanced breast and gastric or gastro-esophageal tumors. This study shows an important activity in HER2 overexpression tumors, however results from phase II and III clinical trials are still to come.

### **Epidermal Growth Factor Receptor (EGFR) Inhibition**

EGFR expression is an independent worse prognostic factor in gastric cancer and is overexpressed by 30 to 50% of these tumors constituting a potential therapeutic target.

Cetuximab (EXPAND trial) and panitumumab (REAL3 trial) failed to demonstrate benefit in advanced gastro-oesophageal tumors. Those trials did not select patients by EGFR expression.

The anti-EGFR antibody nimotuzumab, in a phase II trial in advanced GC, did not increase OS or PFS in the overall population, but on those with EGFR overexpression it had a significant benefit, which increased interest in selecting patients by EGFR status for EGFR-targeting therapies in GC. Also, retrospective biomarker analyses of a phase III clinical trial testing Gefitinib on oesophageal cancer progressing after chemotherapy (COG trial) suggest that a subpopulation with EGFR overexpression may benefit from anti-EGFR therapy. Thus, EGFR overexpression might be a biomarker to select anti-EGFR treatment in GC, and more studies are needed to evaluate that.

### **Immune Checkpoint Inhibitors**

As stated there is a big rational and potential for the utility of immune-checkpoint inhibitors (ICI) in GC, in monotherapy or in different combination regimens.

A phase I/II study combining ipilimumab and nivolumab led to sustained responses and long-term overall survival in heavily pretreated patients with advanced gastric, esophageal and GEJ cancers.

Different trials are testing different ICI combinations, such as nivolumab with mogamulizumab (antibody targeting chemokine receptor (CCR4)), or LAG525 (targets LAG-3) with anti-pd1 spartalizumab.

Some cytotoxic agents might increase tumor immunogenicity, by different mechanisms.

A phase 3 clinical trial is still recruiting to test nivolumab and ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin. Pembrolizumab is also being tested in combination with chemotherapy in first line gastric or GEJ adenocarcinoma and perioperative setting.

Despite rare, it is known distant tumor regression, after radiotherapy – the so-called abscopal effect [54], which might be due to an immune system activation against the tumor. Different pathways could contribute to radiotherapy immunomodulatory effects, such as exposition of neo-antigens, activating leukocytes and recruitment of immune cells into the tumor microenvironment or increasing pro-inflammatory cytokines. There are some studies testing the potential synergic combination between immunotherapy and RT in GC.

The ongoing research will probably bring more evidence to the benefit of different immunotherapy combinations, schemes of treatment as well as better patient selection.

**PIK3CA**

PIK3CA and AKT are downstream effectors of RAS. From the TCGA report, 80% of EBV tumors and 42% of MSI tumors have a PIK3CA mutation, suggesting that this pathway is a possible target for new treatments in gastric cancer. Some AKT inhibitors, such as afuresertib, ipatasertib (GDC-0068), MK2206 or AZD5363, are being tested in GC and the results are forthcoming.

**PARP**

PARP inhibition has an important role in BRCA-associated breast and ovarian cancers and might have additional importance in other cancers, such as gastric adenocarcinoma. Higher PARP-1 expression could be found in GC, and that might be related to more advanced disease and worse prognosis. After some promising results in a phase 2 clinical trial, in the GOLD phase 3 clinical trial, the PARP inhibitor olaparib did not significantly increase OS in patients with advanced gastric cancer, but other trials to address PARP inhibitors in GC are still ongoing.

**Fibroblast Growth Factor Receptor (FGFR)**

Interference with Fibroblast Growth Factor Receptor (FGFR) pathway, such as gene amplification, chromosomal translocation or mutations, is associated with tumor initiation, survival, proliferation or invasion, particularly in diffuse-type cancers, such as with GC.

Some drugs, such as dovitinib, foretinib or pazopanib are multiTKI, in which inhibition includes FGFR.

There are already some clinical trials targeting FGFR in GC. It is not yet known if targeting only one FGFR will have positive results in GC, but there might be a place for multiTKIs that inhibit FGFR along with other kinase pathways.

**Multiple-Choice Questions****1. What are the geographic areas with higher incidence of Gastric Cancer?**

- (A) Western World
- (B) United States of America
- (C) Eastern Asia and South Europe
- (D) France and Belgium
- (E) Canada and Russia

The highest rates are reported in Eastern Asia, Eastern Europe, and South America, with 50% occurs in Eastern Asia. Some other geographic areas also have high incidence including Southern Europe, particularly Portugal.

**2. Which bacteria is a well-known strong risk factor for Gastric Cancer?**

- (A) Escherichia coli
- (B) Clostridium difficile
- (C) Pseudomonas aeruginosa
- (D) Helicobacter Pylori
- (E) Klebsiella Pneumoniae

- H. pylori is classified as a definite carcinogen by The World Health Organization's International Agency for Research on Cancer and has been associated with an increased risk of development of gastric adenocarcinoma.
- H. pylori infection triggers inflammation at the corpus mucosa resulting in atrophy and intestinal metaplasia that precedes development of dysplasia then carcinoma.

**3. What are the well-known risk factors for development of Gastric Cancer?**

- (A) Swimming and football
- (B) Fresh vegetables and fresh water
- (C) Previous gastric surgery and tobacco
- (D) Low body mass index
- (E) Bread

There is an increased risk of gastric cancer after gastric surgery. This risk is associated with the reason of initial surgery and the type of reconstruction, in addition to the interval between initial gastric surgery and the development of a gastric cancer. This risk has been found to be associated with longer duration of follow-up after gastric surgery.

**4. What is the rate of familiar component in Gastric Cancer?**

- (A) 20–30%
- (B) 40–60%
- (C) 0–1%
- (D) 5–10%
- (E) 10–20%

Most gastric cancers are sporadic, aggregation within families occurs in around 10% of cases. Familial gastric cancer includes at least three principle syndromes: hereditary diffuse gastric

cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC).

**5. What are the molecular subtypes defined by The Cancer Genome Atlas TCGA in Gastric cancer?**

- (A) Microsatellite-unstable, mesenchymal-like, p53-active or p53-inactive types.
- (B) EBV positive, Helicobacter positive, diffuse and intestinal
- (C) p53-active; p53-inactive; EBV; microsatellite-unstable
- (D) EBV positive, epigenetic stable, p-53 positive, p-53 negative
- (E) Chromosomally instability, microsatellite-unstable, genomically stable and EBV positive

Based on data from 295 tumors, by using six genomic and molecular platforms, the TCGA network classified gastric cancer into four subtypes: Epstein-Barr virus

positive tumors, microsatellite instable tumors, genomically stable tumors, and tumors with chromosomal instability

**6. Based on TCGA molecular analysis, which subtype has a better prognosis?**

- (A) Genomically stable
- (B) EBV positive
- (C) Diffuse tumor
- (D) Microsatellite-unstable
- (E) Chromosomal instability

EBV infection status was a prognostic factor, in addition to the stage, age, anatomic subsite, and degree of differentiation. Results from a pooled analysis including 13 studies, including 4599 patients, found that EBV-positive GC was associated with better prognosis, with significant better survival (median survival of 8.5 years versus 5.3 years for EBV-negative patients). This better prognosis may be explained by decreased nodal involvement, reduced residual disease and younger age in this subgroup.

**7. Which exam is very useful for assessing small lesions, depth of invasion of primary GC and local lymph nodes?**

- (A) Pet
- (B) Computed tomography (CT) scan
- (C) Endoscopic ultrasonography (EUS)
- (D) External ultrasonography
- (E) Physical examination

EUS is the most reliable exam to evaluate the depth of tumor invasion especially for early T1 lesions and provides more accurate prediction of T stage than does CT. EUS staging versus histopathology was compared in a systematic review and the results found that sensitivity and specificity rates for distinguishing T1 from T2 cancers with EUS were 85% and 90% respectively and 86% and 90% for T1/2 versus T3/4 tumors respectively. EUS also allows more accurate nodal staging by allowing guided fine needle aspiration of suspicious nodes.

**8. How many (minimum) lymph nodes should be assessed for adequate staging during surgery?**

- (A) 5
- (B) 10
- (C) 15
- (D) 20
- (E) 30

The UICC/AJCC TNM classification recommends excision of a minimum of 15 lymph nodes to allow reliable N staging. Multiple prospective randomized trials both in Asian and Western populations have failed to show an overall survival benefit with extended lymphadenectomy (D2, D3 versus D1).

**9. The Lauren classification first published in 1965, divided gastric adenocarcinomas into:**

- (A) Intestinal and esophagic
- (B) Diffuse and squamous
- (C) Squamous and intestinal
- (D) Intestinal and diffuse
- (E) Neuroendocrine and diffuse

Lauren divided the histology of gastric cancer into two groups including the intestinal type and the diffuse type. Later, the indeterminate type was included to describe an uncommon histology. Most studies demonstrated that the intestinal type is the most common, followed by the diffuse and then indeterminate type.

**10. What is the percentage of adenocarcinomas in Gastric Cancer?**

- (A) 20%
- (B) 40%
- (C) 50%
- (D) 60%
- (E) 90%

Gastric adenocarcinoma originates from glandular epithelium of the gastric mucosa, and comprises approximately 90% of the total number of gastric malignancies. The other 10% GC are commonly gastrointestinal stromal tumors (GISTs), lymphomas and neuroendocrine tumors.

**11. The MAGIC trial, in resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus, showed the benefit of:**

- (A) Radiotherapy vs surgery
- (B) Radiotherapy vs perioperative chemotherapy
- (C) Radiotherapy vs placebo
- (D) Surgery with perioperative chemotherapy vs surgery
- (E) Surgery vs placebo

The MAGIC trial assigned patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus to either perioperative chemotherapy and surgery or surgery alone. And it has shown that perioperative chemotherapy with ECF significantly improved progression-free and overall survival.

**12. Which drug is NOT a validated option for perioperative chemotherapy in resectable gastric cancer?**

- (A) Capecitabine
- (B) Docetaxel
- (C) Bevacizumab
- (D) Oxaliplatin
- (E) Cisplatin

Until now, there is no study that showed that adding bevacizumab to perioperative chemotherapy provides a benefit for patients with resectable disease. The MAGIC-B trial is randomizing patients to receive the perioperative regimen administered in the original MAGIC trial with or without the VEGFA inhibitory monoclonal antibody bevacizumab. This study will provide critical information regarding optimal timing and treatment regimen.

13. **Which protocol is validated** in peri-operative strategy for gastric cancer?

- (A) Docetaxel, oxaliplatin, leucovorin and 5-FU
- (B) Doxetaxel, oxaliplatin, bevacizumab and sunitinib
- (C) Docetaxel, olaparib, bevacizumab and sunitinib
- (D) Docetaxel, cisplatin, bevacizumab and nivolumab
- (E) Docetaxel, oxaliplatin, sunitinib and pertuzumab

The FLOT4-AIO trial is multicenter randomized phase 3 trial which showed that perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) improved outcome in patients with resectable gastric and GEJ cancer compared to periop ECF/ECX.

14. **In first line treatment for metastatic gastric cancer with HER2 overexpression, the ToGA trial showed the benefit of:**

- (A) Trastuzumab plus pertuzumab vs chemotherapy alone
- (B) Pertuzumab vs transtuzumab
- (C) Trastuzumab plus chemotherapy vs chemotherapy alone
- (D) Trastuzumab plus chemotherapy vs TDM1
- (E) Trastuzumab alone vs chemotherapy alone

TOGA trial demonstrated that adding Trastuzumab to chemotherapy provides an advantage in overall survival in patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer.

15. **Regarding targeting angiogenesis in Gastric Cancer, choose THE MOST CORRECT answer**

- (A) Apatinib showed significant benefit in first line metastatic gastric cancer in European and North American population
- (B) Bevacizumab showed overall positive results on AVATAR and AVAGAST phase III clinical trials in advanced gastric cancer
- (C) Bevacizumab with docetaxel is the gold standard treatment for metastatic gastric cancer
- (D) Ramucirumab demonstrated benefit in the second-line treatment of advanced GC following the REGARD and RAINBOW clinical trials.
- (E) There are no clinical trials that showed any type of benefit from targeting angiogenesis in gastric cancer

REGARD trial is a multicentric trial, that demonstrated a benefit in overall survival with Ramucirumab compared to BSC in patients with advanced gastric or gastroesophageal junction cancer who progressed after chemotherapy.

The RAINBOW trial showed that Ramucirumab plus paclitaxel leads to an advantage in overall survival compared to paclitaxel alone in patients who had disease progression after chemotherapy.

**16. Regarding immune checkpoint inhibitors in Gastric Cancer, choose the WRONG answer:**

- (A) The presence of high somatic mutations, PDL1 expression, MSI-H and mismatch repair deficiency raises a rationale for the use of immune checkpoint inhibitors in GC.
- (B) The KEYNOTE-061, that investigated pembrolizumab in second line treatment for patients with advanced gastric or GEJ adenocarcinoma did not meet its primary endpoint of overall survival.
- (C) Pembrolizumab was approved by FDA on unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment, regardless of tumor histology.
- (D) Nivolumab and Pembrolizumab are approved on stage I and stage II gastric cancer.
- (E) A phase I/II clinical trial combining ipilimumab and nivolumab led to durable responses and long-term overall survival in heavily pretreated patients with advanced gastric, esophageal and GEJ cancers.

Pembrolizumab and Nivolumab are not approved in early stages of GC: The FDA has approved pembrolizumab for the treatment of patients with PD-L1–positive recurrent or advanced gastric or gastroesophageal junction adenocarcinoma who have received 2 or more lines of chemotherapy, including fluoropyrimidine- and platinum-containing chemotherapy based on the phase II KEYNOTE-059 study. The FDA also approved Pembrolizumab on unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, regardless of tumor histology.

Regarding Nivolumab, it has been approved only in Japan for the treatment of unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy based on ATTRACTION-2 trial.

**17. Regarding future treatments for Gastric Cancer, choose the WRONG answer:**

- (A) A biomarker evaluation of AVAGAST trial showed high plasma VEGF-A and low tumor neuropilin-1 as potential biomarker candidates for predicting clinical outcome in patients with advanced gastric cancer treated with bevacizumab.



- (B) Trastuzumab deruxtecan (DS-8201) showed tumor activity in patients with advanced breast and gastric or gastro-esophageal tumors.
- (C) EGFR expression is an independent worse prognostic factor in gastric cancer, is overexpressed by 30 to 50% in these tumors, thus is a potential target in GC.
- (D) Cetuximab (EXPAND trial) and panitumumab (REAL3 trial) showed already significant clinical benefit in metastatic gastric cancer.
- (E) The presence of high somatic mutations, PDL1 expression, MSI-H and mismatch repair deficiency raises a rationale for the use of immune check-point inhibitors in GC.

EXPAND and REAL trials showed that the addition of Cetuximab or Panitumumab to chemotherapy does not increase survival and cannot be recommended for use in an unselected population with advanced oesophagogastric adenocarcinoma.

**18. From all new cases of Gastric cancer in World, how many occur in Eastern Asia?**

- (A) 10%
- (B) 20%
- (C) 30%
- (D) 50%
- (E) 90%

the highest incidence rates are observed in East Asia, East Europe, and South America with more than 70% of cases occur in developing countries and 50% occurs in Eastern Asia.

**Answers:**

- 1-(C); 2-(D); 3-(C); 4-(D); 5-(E); 6-(B); 7-(C); 8-(C); 9-(D); 10-(E); 11-(D); 12-(C); 13-(A); 14-(C); 15-(D); 16-(D); 17-(D); 18-(D)

**Clinical Case**

Mr. Silva is a 65 years old Portuguese fisherman, married and father of two sons and four grandchildren. After 6 months of anorexia with progressive loss of weight (8 kg in 6 months), his wife finally convinced him to consult his family doctor. Dr. Aveiro was immediately concerned when he saw Mr. Silva skinnier and pale. He decided to proceed with a careful history taking and physical examination. Mr. Silva presented indigestion with asthenia and darker stools few days before his consultation. Dr. Aveiro confirmed that he is an active smoker and alcohol drinker, he takes daily aspirin as cardio-protector, and has no other major relevant medical or familiar history. Physical examination, found a patient with Performans status (PS) 1 with epigastric painful mass and the digital rectal examination objectived melena. Routine laboratory parameters showed anemia without other abnormalities. The patient underwent an endoscopy which has revealed an ulcerated mass located on the cardia and multiple biopsies were performed. The histopathological examination concluded a moderately differentiated adenocarcinoma. Mr. Silva and his family were shocked with the diagnosis, and one of his sons decided to stop his job for

some months in order to help his father. The patient was referred to the oncology center in his region, where he underwent a thoraco-abdomino-pelvic computed tomography which showed a localized gastric tumor respecting adjacent structures and without distant metastases. The EUS was performed and showed a tumor penetrating the subserosal connective tissue without invasion of visceral peritoneum or adjacent structures, and only one regional lymph node was suspicious. A staging laparoscopy and peritoneal cytology did not found metastasis. Thus, Mr. Silva was diagnosed with a T3 N1 M0, stage III gastric adenocarcinoma. The clinical case was discussed on a multidisciplinary meeting, and the decision was to proceed with surgery with peri-operative chemotherapy after patient's consent. The patient received 4 cycles of pre-operative chemotherapy based on FLOT regimen (docetaxel 50 mg/m<sup>2</sup>, oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 200 mg/m<sup>2</sup>, and 5-FU 2600 mg/m<sup>2</sup> as 24-hour infusion) with a week postponement of treatment during this period due to a febrile neutropenia, but no other significant toxicity. Then he underwent an RO total gastrectomy with D1+ lymph node dissection, which revealed an ypT2-N0 adenocarcinoma. He received a post-operative chemotherapy based on 4 cycles of the same protocol, without major toxicity. After 2 years of follow-up, an abdominal CT showed multiple liver metastases and the PET/CT also confirmed the presence of lung metastases in addition to hepatic lesions. A liver biopsy confirmed the gastric origin and Immunohistochemistry showed a positive staining for HER2 (score 3), PDL1 > 50%, and MSI-H. He started Cisplatin-5FU-Trastuzumab, but after completing the 6 cycles of chemotherapy, on CT scan it was diagnosed progression of disease. After multidisciplinary meeting, it was given to Mr. Silva the option of Ramucirumab with paclitaxel or going to a clinical trial with an anti-pd1 drug. Mr. Silva accepted to be enrolled in the anti-pd1 drug clinical trial, and after 6 weeks of treatment during follow up, he was found with G2 asthenia, and a small increase on liver lesions on CT scan. It was decided to keep with treatment and after 12 weeks there was an objective partial response, still maintained 12 months later, with good tolerance.

Q1: For this patient diagnosed initially with localized gastric adenocarcinoma (T3N1M0), is surgery alone enough to treat appropriately the patient?

A1: Perioperative chemotherapy with ECF/ECX demonstrated better outcomes in terms of disease free survival and overall survival compared to surgery alone in MAGIC trial. Then perioperative chemotherapy with FLOT regimen improved survival in patients with resectable gastric cancer compared to periop ECF/ECX in the FLOT4 trial. Therefore it is the new standard in this setting.

Q2: is it mandatory to test for Her2 expression and what is the therapeutic impact?

A2: Yes, because 9 to 23% of gastric cancers overexpress Her2 and the TOGA trial showed that Trastuzumab in combination with chemotherapy provides benefit in overall survival compared to chemotherapy alone. Therefore, it is a new standard option for patients with HER2-positive advanced gastric cancer.

Q3: what is the appropriate therapeutic option in later lines for this patient who had metastatic gastric adenocarcinoma with high levels of microsatellite instability (MSI-H) and expressing PDL1?

A3: A possible option for treatment at progression for patients with advanced tumors with high levels of microsatellite instability (MSI-H), deficient mismatch repair (dMMR), or programmed cell death ligand 1 (PD-L1) overexpression is immunotherapy with pembrolizumab which is an immune checkpoint inhibitor that targets the programmed cell death receptor 1. Regarding timing of administration of pembrolizumab, it has been approved by FDA after two or more lines of systemic chemotherapy. However, some clinicians prefer its earlier administration for second-line treatment.

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# Chapter 16

## Colon Cancer



**Pamela Carvalho Muniz, Hakaru Tadokoro, Ramon Andrade De Mello, and Nora Manoukian Forones**

**Abstract** Colon cancer ranks worldwide the second place in prevalence among men (10%) and third place among women (9.2%) (GLOBALCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012, 2012). Although well-established diagnostic methods are indicated for the early diagnosis of the disease, the access and adherence to these screening programs is a global problem. The knowledge of its etiology, molecular changes and pathophysiology will introduce new diagnostic methods with better population reach and new treatments based on specific targets can transform the history of colorectal cancer. This chapter aims to discuss general aspects of colon cancer, its etiology, diagnostic methods and therapeutic possibilities according to its staging.

**Keywords** Colon cancer · Immunotherapy · MSI

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## 16.1 Introduction

Colon cancer ranks worldwide the second place in prevalence among men (10%) and third place among women (9.2%) [1].

Although well-established diagnostic methods are indicated for the early diagnosis of the disease, the access and adherence to these screening programs is a global problem.

The knowledge of its etiology, molecular changes and pathophysiology will introduce new diagnostic methods with better population reach and new treatments based on specific targets can transform the history of colorectal cancer. This chapter aims to discuss general aspects of colon cancer, its etiology, diagnostic methods and therapeutic possibilities according to its staging.

## 16.2 Etiology

The etiology of colorectal cancer comprises a very complex spectrum encompassing environmental factors, genetic and biomolecular changes [2].

Among sporadic cases, we have established direct relationships with some risk factors such as obesity, red meat consumption, obesity, smoking and alcoholism, as well as family or individual history of CCR, polyps and inflammatory bowel diseases [3].

It was first described the tumorigenesis model of colorectal carcinoma through the adenoma carcinoma sequence, establishing that the pre-neoplastic lesions were a set of genetic alterations that over time would determine the transformation of benign lesions into malignant lesions [4].

Numerous molecular alterations are being studied and their knowledge has even allowed specific therapeutic choices for some of these subtypes. One of the molecular pathways, and also the most frequent one, is the chromosomal instability (CIN), whose alterations in the genome itself lead to the loss of heterozygosity, such as the adenomatous polyposis (APC) gene mutation, which is germinative (Adenomatous Polyposis Syndrome) or sporadic [5]. Another example is the mutation of the RAS gene (codons 12 and 13 mainly) that culminates in uncontrolled cell proliferation [5].

Another well-studied molecular spectrum is the DNA Mismatch Repair pathways. Mutations in genes of this pathway (MLH1, MSH2, PMS2, PMS1, MLH3, MSH3, MSH6) lead to modifications in DNA sequences generating so-called microsatellite instability, which accounts for 15% of CCRs, 12% of which are attributed to Lynch's Syndrome [6].

There may also be inactivation of tumor suppressor genes or genes from DNA repair mechanisms due to the methylation of cytosine-guanine islands (CIMP), also described in the molecular genesis of CCR [7].



### 16.3 Clinical Presentation

The clinical presentation most commonly associated with the patient diagnosed with colon cancer includes specific organ and systemic signs and symptoms. It is not uncommon for the patient to begin to present such changes months before the diagnostic completeness. Among the most frequent ones we can mention the alteration of intestinal habit (diarrhea or obstipation), intestinal bleeds, stool thinning, abdominal pain, anemia, weight loss, fatigue, inappetence. Tumor mass in the right flank or hypochondrium associated to diarrhea and anemia is a characteristic of right colon cancer. Hepatomegalia and ascites may also occur and are signs of advanced disease [8].

### 16.4 Diagnosis

Fecal occult blood test (FOBT) may be used as a screen method and can be done by the guaiac method or by the immunochemical method. The last one is more specific because excludes non-human hemoglobin and bleeding from the upper gastrointestinal tract, guaranteeing specificity of 79% and sensitivity of 94% [9, 10].

Colonoscopy is the examination that allows the direct evaluation of the colon allowing biopsy and small therapeutic interventions as polypectomies or mucosectomies of small cancers. However this exam need a hard colon cleaning with laxatives and an experienced examiner [10].

### 16.5 Screening

The decrease in the incidence of colon cancer can be impacted by educational campaigns aimed at health promotion, implementation of screening tests for early detection in both, the general population and the population at known risk such as those meeting criteria for familial genetic syndromes [2]

For the general population, the US Preventive Services Task Force (USPSTF) recommends screening for colorectal cancer with FOBT, sigmoidoscopy, or colonoscopy for the population over 50 and up to age 75, with annual interval for FOBT, every 5 years (with FOBT every 3 years) for sigmoidoscopy and every 10 years for colonoscopy [11]. New screening tests on DNA testing DNA mutation had been approved by FDA in 2014 [12].

### 16.6 Staging and Prognosis

The pathologic and clinical stage is done by evaluation of the tumor extension, lymph nodes and metastases. At 2017, the American Joint Cancer Committee (AJCC) Cancer Staging Manual published its eighth edition, as shown in Table 16.1 [13].

**Table 16.1** TNM staging according to AJCC 8th Edition

Clinical Stage (CS)	T	N	M
0	Tis	N0	M0
I	T1, T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1, T2	N1/N1c	M0
IIIA	T1	N2a	M0
IIIB	T3, 4	N1/N1c	M0
IIIB	T2, T3	N2a	M0
IIIB	T1, T2	N2b	M0
IIIC	T4a	N2a	M0
IIIC	T3, T4a	N2b	M0
IIIC	T4b	N1-N2	M0
IV	Any T	Any N	M1a
IV	Any T	Any N	M1b
IV	Any T	Any N	M1c

We classified each individual as to tumor size (T), number of lymph nodes affected (N) and presence of metastases (M), as below [13]:

- T0: no evidence of primary tumor
- Tis: in situ and intramucosal carcinomas
- T1: invades the submucosal layer
- T2: invades the muscular layer itself
- T3: they surpass the own muscular until the pericorectal tissues
- T4: invades the visceral peritoneum, adjacent organs and/or structures
  - T4a: involvement of the visceral peritoneum (including perforation, invasion by continuity in areas of inflammation on its surface)
  - T4b: invades or adheres to adjacent organs or structures.
- Nx: lymph nodes not accessed
- N0: do not present metastases for regional lymph nodes
- N1: involvement of 1–3 regional lymph nodes (greater than or equal to 0.2 mm)
  - N1a: a regional lymph node
  - N1b: 2 or 3 lymph nodes
  - N1c: no lymph node is positive but there is tumor deposition in the subserosa, in the mesentery or in pericolic, non-peritonized peri or mesorectal tissue.
- N2: 4 or more regional lymph nodes
  - N2a: 4 to 6 regional lymph nodes
  - N2b: 7 or more regional lymph nodes.
- M0: no distant metastases
- M1: one or more sites or organs, including the peritoneum

- M1a: a single site or organ without peritoneal disease,
- M1b: 2 or more sites or organs also without peritoneal disease
- M1c: when there is exclusive peritoneal involvement or not.

The thorax and abdominal computadorized tomography (CT) may be done to evaluate the tumor extension and metastases. Magnetic resonance of the pelvis had a higher sensibility to evaluate tumoral extension and positive lymph nodes compared to CT Scan in rectal cancer. PET CT can help on colorectal cancer staging but is not mandatory. The PET CT Scan is more indicated to evaluate patients with elevated CEA and normal CTs [14].

## 16.7 Treatment

### 16.7.1 *Surgical Approach*

The curative intention of the treatment of colon cancer is concretized with the surgical resection of the tumor lesion, which is mostly possible in the stages I–III. of the disease. Right hemicolectomy, left hemicolectomy and sigmoidectomy may be done for right, left and sigmoid cancer.

If the disease is unresectable or the patient is inoperable, chemotherapy should be considered. In progress, the trial FOxTROT aims to respond to the real benefit of preoperative chemotherapy in the locally advanced disease scenario using fluoracil, oxaliplatin with or without panitumumab [15].

In the cases that were candidates for an immediate surgical approach, when the laparoscopic approach was compared to open surgery, there was no survival impairment with the minimally invasive technique, plus its short-term benefits [16].

### 16.7.2 *Adjuvant Chemotherapy*

From CS II, adjuvant chemotherapy had to be discussed according to risk factors and microsatellite instability (MSI).

If you choose to perform adjuvant chemotherapy, this should start up to 8 weeks after surgery, with a known loss of benefit every 4 weeks that add up [17, 18]. The duration of treatment is 6 months, with a recent non-inferiority study raising the discussion about the reduction of this time to 3 months in selected groups, not yet established [19].

#### 16.7.2.1 **Clinical Stage II**

After surgical resection, some clinical and pathological criteria help to predict a higher risk of recurrence and, consequently, a greater benefit for adjuvant chemotherapy: low lymph node sampling (less than 13 lymph nodes), venous and

perineural invasion, patients over 50 years, T4 tumors with microsatellite stability, preoperative CEA [20–23].

With the advancement of the molecular profile studies it has been possible to select within the EC II those patients in whom only surgery is able to guarantee a satisfactory survival. The evaluation of microsatellite instability (Mismatch Repair gene proficiency or deficiency) allows us to say that ECII patients with MSI have a better prognosis and do not require adjuvant chemotherapy [24].

Studies such as QUASAR trial have already demonstrated the modest benefit of adding chemotherapy (fluoruracil and leucovorin) to EC II patients [25]. When assessing whether combination regimens with oxaliplatin would increase survival benefits for clinical stage II, this has not been demonstrated and may be considered in high-risk disease (low lymph node sampling, venous and perineural invasion, patients over 50 years, T4 tumors with microsatellite stability, high preoperative CEA) [26–28].

### 16.7.2.2 Clinical Stage III

In the clinical stage III, the addition of adjuvant chemotherapy is recommended, in infusion regimens (FOLFOX4) or bolus (FLOX), in combination with fluoracil and oxaliplatin [28, 29]. Combinations with irinotecan, coming from the metastatic scenario, besides not adding benefit in the adjuvant, were shown to be deleterious [30].

The X-ACT trial randomized EC III patients for the use of capecitabine (oral fluoropyrimidine) or 5FU/Leucovorin (Mayo Clinic regimen) and demonstrated comparable clinical benefit, as well as efficacy, cost and safety for the use of oral medication, making it the plausible option in the combination [31]. Further studies have demonstrated the benefit of progression-free survival and overall survival in later long-term analysis for the use of the XELOX regimen in the adjuvant setting [32, 33].

Other medications brought from the metastatic setting also failed to confirm their benefit in adjuvant therapy, such as bevacizumab [34] and cetuximab [35].

As for the elderly population, between 70 and 75 years there was no survival benefit with the addition of oxaliplatin [27]. In another study also evaluating adjuvant in the elderly population, here considered over 65 years, it was demonstrated that patients who did not complete at least 5 months of chemotherapy had worse survival compared to those who did 5–7 months of treatment [36].

Anti EGFR and anit-VEGF drugs had not benefit on adjuvant setting.

### 16.7.3 Metastatic Disease (EC IV)

Although the number of systemic therapies available for metastatic colon cancer has not increased and fluorouracil remains the preponderant pillar of treatment, better molecular understanding and possible therapeutic sequences as well as

multidisciplinary approaches that allow resection of metastases, there has been increased survival rates and even cure rates for some patients [37].

From the molecular point of view the study of the presence or absence of the RAS gene mutation is a predictive biomarker. In patients with RAS mutation, the use of medications such as cetuximab and panitumumab targeting EGFR does not add benefit [38, 39].

In contrast to the adjuvant context, the evaluation of microsatellite instability may predict benefit of the use of immune checkpoint inhibitors, such as pembrolizumab, recently released in this context [40], and nivolumab evaluated in a phase II study [41].

### 16.7.3.1 Systemic Chemotherapy of Unresectable or Metastatic Disease

As alternatives to the first line in systemic treatment, combinations of oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) with a fluoropyrimidine (oral or intravenous) were shown to be better than fluoropyrimidine monotherapy [42, 43]

Regarding the order of the therapeutic lines, several studies evaluated the sequence to be performed that offered greater overall survival to the patients. The GERCOR study compared the first line of FOLFIRI followed by FOLFOX6 in disease progression, versus the opposite sequence, demonstrating that both offered comparable efficacy and prolonged survival, with a major difference in toxicity profiles [44].

As regards combinations of chemotherapeutic regimens to available antibodies, the FIRE-3 study evaluated the use of FOLFIRI with Cetuximab or Bevacizumab, and although it showed no difference in response rate between the schemes, the overall survival advantage suggests the use of cetuximab in the first line [45].

In a first-line study comparing regimens with irinotecan (FOLFIRI, mIFL and XELIRI), the oral fluoropyrimidine scheme had lower PFS (7.6 months vs 5.9 months vs 5.8 months,  $p = 0.015$ ) and higher adverse effects [46].

Some experimental studies demonstrated that anti VEGF drugs in second line after anti-EGFR offer more benefits than the inverse.

In the wild-type RAS patients, the combination of FOLFOX4 and Panitumumab, an anti-EGFR monoclonal antibody, was also evaluated, demonstrating acceptable tolerance and benefit in PFS (9.6 months vs 8 months,  $p = 0.02$ ) [47].

For the second line of treatment of wild RAS patients, we attempted to evaluate in a recent study the sequence of Irinotecan with Cetuximab and after further progression, FOLFOX4 or reverse order in those patients who progressed to the use of FOLFIRI and Bevacizumab in the first line, without significant difference in PFS but suggesting less activity of cetuximab in the second line [48].

In the case of patients who failed the first line of oxaliplatin treatment, revising the use of oral fluoropyrimidine, a recent study compared the combination regimens with capecitabine and irinotecan (XELOX followed by XELIRI) and fluoracil, leucovorin and irinotecan (FOLFOX followed by FOLFIRI) demonstrating similar efficacy among them [49].

Also in the second line, a comparison study between FOLFIRI and Ramucirumab, anti-VEGFR antibody, and FOLFIRI plus placebo, after failure of bevacizumab, fluoropyrimidine and oxaliplatin. The study had overall survival gain for the combination (13.3 months vs. 11.7 months,  $p = 0.02$ ) [50].

Another anti-VEGF agent, aflibercept, was tested in the second line after failure of oxaliplatin regimens in a phase III study associated with FOLFIRI compared to placebo and achieved overall survival gain (13.5 months vs 12.6,  $p = 0.003$ ) [51].

As a therapeutic option for patients who have failed previous lines, regorafenib presents with overall survival gain (from 5 to 6.4 months,  $p = 0.0052$ ) in a phase 3 study, making possible the use of this inhibitor multikinase with acceptable toxicity profile and its most common adverse effects were fatigue (48.1%), diarrhea (36.7%), hypertension (36.7%) and hand foot syndrome (17%) [52, 53].

More studies have sought alternatives for patients who have failed at least two previous regimens. The RECURSE study compared TAS-102, an oral nucleotide analogue with placebo, and demonstrated overall survival benefit for the medication [54].

### 16.7.3.2 Conversion Therapy

The choice of the best chemotherapy regimen to approach initially unresectable lesions is extensively studied in some trials, aiming at better response rates so that there is ultimately a possibility of resection. TRIBE trial describes the role of the combination of FOLFIRINOX and Bevacizumab (compared to FOLFIRI and Bevacizumab), which significantly increased the response rate between groups (53.1% vs 65.1%), although this did not correlate with higher rates resection R0 [55].

Combination of chemotherapy (FOLFOX6 or FOLFIRI) with cetuximab was evaluated in a randomized phase II study, with higher rates of response and resectability in both groups, more prominent in wild-type RAS patients [56].

### 16.7.3.3 Treatment of the Resectable Disease

Although it is an option to perform surgery as an initial approach to resectable metastatic disease, studies have added the possibility of performing perioperative chemotherapy. The EPOC study randomized patients for surgery or for FOLFOX4 (6 cycles before and 6 cycles after surgery) and although without overall survival gain even in a long follow-up study [57], it presented a gain of 9.2% in disease free survival (33.2%–42.4%) in the resected group [58]. The attempt to add cetuximab to the chemotherapy regimen of patients with wild-type RAS was ineffective in the New EPOC study, and so is not recommended so far [59].

## 16.8 Follow Up

For patients who underwent follow-up colonoscopy, the recommendation for a new one depends on the findings of the examination itself, namely [60]:

**Table 16.2** NCCN recommendation for follow-up after treatment of colon neoplasia

Clinical stage	Follow-up exam	Interval
<b>Clinical Stage I</b>	Colonoscopy	In 1 year. Adenoma: 1 year. No adenoma: at 3 years and after every 5 years.
<b>Clinical Stages II e III</b>	Clinical Evaluation	Every 3–6 months for 2 years and then every 6 months up to 5 years.
	CEA	Every 3–6 months for 2 years and then every 6 months up to 5 years.
	CT Thorax and Abdomen/Pelvis	Every 6–12 months up to 5 years.
	Colonoscopy	In 1 year. Adenoma: 1 year. No adenoma: at 3 years and after every 5 years.
<b>Clinical Stage IV</b>	The same as stages II and III	Similar to stages II and III, except interval for CTs, here 3–6 months in the first 2 years.

- No polyps or hyperplastic polyps: repeat in 10 years;
- Serrated polyps: repeat in 1 year;
- Injuries less than 1 cm, in proximal colon and without dysplasia: repeat in 5 years;
- Injuries greater than or equal to 1 cm, with dysplasia or serrated adenoma: repeat in 3 years;
- Low risk adenomas (less than 1 cm, 1–2 tubular adenomas): repeat between 5 and 10 years
- High risk adenomas:
  - If 3–10 adenomas or larger than 1 cm being villous or tubular or dysplasia important: repeat in 3 years;
  - If more than 10 adenomas: repeat before 3 years.

The National Comprehensive Cancer Network (NCCN) provides follow-up recommendations according to neoplasm staging (Table 16.2) [14].

### Questions

1. **Man, 63 years old presented with intestinal constipation associated with abdominal pain. He sought a Gastroenterologist who requested a colonoscopy where it was evidenced a vegetal lesion occupying more than 50% of the intestinal light. He underwent exploratory and laparotomy and the anatomopathological was compatible with moderately differentiated adenocarcinoma invading pericolic fat with 3 positive lymph nodes of 35 averted, and negative surgical margins. Negative systemic staging scans. Regarding the specific postoperative cancer treatment, the most appropriate would be:**
  - (a) Follow up with anual colonoscopy and CTs
  - (b) 5 FU and Leucovorin for 6 months
  - (c) Capecitabine for 6 months
  - (d) FOLFOX and bevacizumab for 6 months
  - (e) FOLFOX for 6 months

**Commentary:** In the clinical stage III, the addition of adjuvant chemotherapy is recommended, in infusion regimens (FOLFOX4) or bolus (FLOX), in combination with fluoracil and oxaliplatin. The duration of treatment is 6 months.

2. **As for the patient above, thinking about risk factors for having developed colon cancer even without a family history of cancer, we could infer:**

- (a) History of smoking
- (b) History of alcoholism
- (c) Diet rich in red meats
- (d) Obesity
- (e) All above are correct

**Commentary:** Among sporadic cases, we have established direct relationships with some risk factors such as obesity, red meat consumption, obesity, smoking and alcoholism, as well as family or individual history of CCR, polyps and inflammatory bowel diseases.

3. **The genetic alteration associated with resistance to cetuximab is:**

- (a) MLH1 Inactivation
- (b) BRAF Mutation
- (c) RAS Mutation
- (d) RAS wild type
- (e) EGFR Mutation

**Commentary:** In patients with RAS mutation, the use of medications such as cetuximab and panitumumab targeting EGFR does not add benefit.

4. **They are not genes related to instability of microsatellites:**

- (a) MLH1
- (b) PMS2
- (c) MLH2
- (d) APC
- (e) MSH2

**Commentary:** The spectrum of the ‘DNA Mismatch Repair pathways’ include mutations in genes such as the following: MLH1, MSH2, PMS2, PMS1, MLH3, MSH3, MSH6, that associate to modifications in DNA sequences generating so-called microsatellite instability. A mutation of the APC gene, germinal or somatic, is associated with adenomatous polyposis syndrome.

5. **What is the gene associated with hereditary non-polypoid colorectal cancer (HNPCC)?**

- (a) MSH2
- (b) MYH
- (c) APC
- (d) STK11
- (e) p53



**Commentary:** HNPCC is an autosomal dominant syndrome, which accounts for about 5% CRCs, due to MLH1 and MSH2 mutations that impair DNA repair functions.

**6. All of the alternatives below are correct except:**

- (a) In the wild-type RAS patients, the combination of FOLFOX and Panitumumab demonstrated benefit in PFS
- (b) As a therapeutic option for patients who have failed previous lines, regorafenib presents with overall survival gain
- (c) TAS-102, an oral nucleotide analogue with placebo, and demonstrated overall survival benefit for the medication
- (d) Aflibercept was tested in the second line after failure of oxaliplatin regimens in a phase III study associated with FOLFIRI, and achieved overall survival gain
- (e) Pembrolizumab is an option for all patients who have failed previous treatment lines, with overall survival gain

**Commentary:** The evaluation of microsatellite instability may predict benefit of the use of immune checkpoint inhibitors, such as pembrolizumab. The studies try to select the group of patients that could benefit from this new therapy and in the scenario of immunotherapy in colorectal cancer it seems that the carriers of microsatellite instability are the ones that benefited the most.

**7. Exploratory laparotomy product/Anatomopathological result: Moderately differentiated adenocarcinoma that invades up to the muscular layer, 37 lymph nodes were dissected, of which two were affected by adenocarcinoma.**

- (a) T3N2a
- (b) T2N1b
- (c) T2N2b
- (d) T3N1b
- (e) T2N1b

**Commentary:** According to AJCC 8<sup>a</sup> edition we call T2 the lesion which invades the muscular layer itself, and N1 the involvement of 1–3 regional lymph nodes (greater than or equal to 0.2 mm). We specifically named N1b when there is involvement of 2–3 lymph nodes.

**8. After surgical resection, some clinical and pathological criteria help to predict a higher risk of recurrence in CSII and, consequently, a greater benefit for adjuvant chemotherapy:**

- (a) Low lymph node sampling
- (b) Venous and perineural invasion
- (c) T4 tumours
- (d) Microsatellite stability
- (e) All above

**Commentary:** After surgical resection, some clinical and pathological criteria help to predict a higher risk of recurrence and, consequently, a greater benefit for adjuvant chemotherapy: low lymph node sampling (less than 13 lymph nodes), venous and perineural invasion, patients over 50 years, T4 tumors with microsatellite stability, preoperative CEA

**9. For the general population, the US Preventive Services Task Force (USPSTF) recommends screening for colorectal cancer with:**

- (a) FOBT, sigmoidoscopy, or colonoscopy for the population over 50 and up to age 75
- (b) FOBT, sigmoidoscopy, or colonoscopy for the population over 60 and up to age 85
- (c) FOBT, sigmoidoscopy, or colonoscopy for the population over 50 and up to age 70
- (d) FOBT, sigmoidoscopy, or colonoscopy for the population over 55 and up to age 70
- (e) FOBT, sigmoidoscopy, or colonoscopy for the population over 50 and up to age 80

**Commentary:** According to the US Preventive Services Task Force (USPSTF), one of the guidelines used for screening the general population, we must do FOBT, sigmoidoscopy or colonoscopy for the population over 50 and up to age 75. The population at high risk for developing colorectal cancer should be submitted to specific guidelines for screening and follow-up.

**10. Which of the following is related to microsatellite instability:**

- (a) MLH1 present, MSH2 present, PMS2 present
- (b) PMS1 present, MLH3 absent, MSH3 present,
- (c) MSH6 present, MSH2 absent, PMS2 present
- (d) PMS1 present, MLH3 present, MSH2 present
- (e) Alternatives b and c

**Commentary:** Direct or indirect study of mutations in DNA repair genes defines whether a tumor is caused by replication errors. If any gene studied is mutated/absent, microsatellite instability is present.

**11. All of the alternatives below are correct except:**

- (a) TRIBE trial describes the role of the combination of FOLFIRINOX and Bevacizumab, which significantly increased the response rate between groups, although this did not correlate with higher rates resection R0
- (b) TRIBE trial describes the role of the combination of FOLFIRINOX and Bevacizumab (compared to FOLFIRI and Bevacizumab), which significantly increased the response rate between groups and was correlated with higher rates resection R0

- (c) The EPOC study randomized patients for surgery or for FOLFOX4 (6 cycles before and 6 cycles after surgery) without overall survival gain even in a long follow-up study
- (d) The EPOC study presented a gain of 9.2% in disease free survival in the resected group
- (e) TRIBE trial describes the role of the combination of FOLFIRINOX and Bevacizumab compared to FOLFIRI and Bevacizumab

**Commentary:** According to the study published in 2015, the TRIBE trial describes the role of the combination of FOLFIRINOX and Bevacizumab (compared to FOLFIRI and Bevacizumab), which significantly increased the response rate between groups (53.1% vs 65.1%) and was correlated with higher rates resection R0

**12. Which of the following statements is correct:**

- (a) Tumors with microsatellite instability may be resistant to treatment with 5 FU
- (b) Patients with defects in DNA repair present poor results with systemic therapy
- (c) Microsatellite instability is a result of chromosomal instability
- (d) Less than 10% of colorectal cancers have high levels of microsatellite instability
- (e) Tumors with microsatellite instability respond very well to 5FU.

**Commentary:** Microsatellite instability research has application in clinical practice, since mutations in the DNA repair genes are associated with better prognosis and resistance to fluoropyrimidine-based therapy, which is the mainstay of the therapeutic base of these tumors.

**13. On staging of metastatic disease according to AJCC 8<sup>th</sup> edition is not correct:**

- (a) M1a: a single site or organ with peritoneal disease
- (b) M1a: a single site or organ without peritoneal disease
- (c) M1b: 2 or more sites or organs also without peritoneal disease
- (d) M1c: when there is exclusive peritoneal involvement or not
- (e) M0: no distant metastases

**Commentary:** According to the 8th edition of AJCC, metastatic disease should be classified as the following description: M0 when there are no distant metastases, M1 when there are one or more sites or organs, including the peritoneum, M1a, when there is a single site or organ without peritoneal disease, M1b when there are 2 or more sites or organs also without peritoneal disease and, finally, M1c when there is exclusive peritoneal involvement or not.

#### 14. Adjuvant chemotherapy in clinical stage II:

- (a) Should start up to 8 weeks after surgery, with a known loss of benefit every 4 weeks that add up
- (b) Should start up to 6 weeks after surgery, with a known loss of benefit every 4 weeks that add up
- (c) Should start up to 4 weeks after surgery, with a known loss of benefit every 4 weeks that add up
- (d) Should start up to 10 weeks after surgery, with a known loss of benefit every 4 weeks that add up
- (e) Should start up to 12 weeks after surgery, with a known loss of benefit every 4 weeks that add up

**Commentary:** Adjuvant chemotherapy should be started within 8 weeks after surgery. Studies demonstrate that the delay of initiation of adjuvant chemotherapy may decrease overall survival.

#### 15. Select the most common mode of spread of colon cancer:

- (a) Hematogenous
- (b) Lymphatic
- (c) Direct extension
- (d) Implantation
- (e) None of the above

**Commentary:** Although there may be dissemination of the disease through several pathways, such as hematogenous, direct extension, implants and lymphatic, the most common is the lymphatic pathway and it is the one who dictates the prognosis that will contribute to subsequent therapeutic decisions, including the supply of adjuvant chemotherapy.

**Answers** 1-e; 2-e; 3-c; 4-d; 5-a; 6-e; 7-b; 8-e; 9-a; 10-e; 11-b; 12-a; 13-a; 14-a; 15-b.

#### Clinical Case and Commented Question

A 51 years old man started an alteration of intestinal habit associated with stool thinning, inappetence and weight loss of 10 kg. On screening exams: positive FOBT and a mass at the splenic angle seen at colonoscopy occupying more than 80% of the lumen of the colon. Biopsy compatible with moderately differentiated adenocarcinoma. Thoracic, abdominal and pelvic CT scans were performed for systemic staging of the disease, presenting two liver lesions in the left lobe of the liver compatible with secondary involvement. The search for the RAS gene mutation was compatible with wild-type RAS.

Patient was submitted to left hemicolectomy, considering important colon obstruction, without postoperative complications. It was then chosen to initiate chemotherapy with FOLFIRI and cetuximab.

Four cycles of chemotherapy were performed and the case was then discussed at a multidisciplinary meeting where resection of liver metastases was proposed. After hepatectomy with uncomplicated postoperative period, chemotherapy was returned for another 3 cycles, with new systemic staging with imaging exams without evidence of disease.

### Questions

1. In the scenario of metastatic disease is the option for polychemotherapy feasible?
2. Based on which study was chosen by the therapeutic apparatus in the case in question?
3. If the patient had a RAS mutation, which conversion therapy option would be feasible based on a phase III study?

### Comments

1. The choice of the best chemotherapy regimen to approach initially unresectable lesions is extensively studied in some trials, aiming at better response rates, so that there is ultimately a possibility of resection. Some robust studies such as TRIBE trial and FIRE trial for example, describes the role of the combination of polychemotherapy and monoclonal antibodies with significantly increased the response rate, making the surgical option possible and aiming to eradicate the disease.
2. Based on the FIRE-3 study, a superiority of the combination FOLFIRI and cetuximab in the wild RAS patients allows us to use it as conversion therapy and resection of metastases aiming at the eradication of neoplastic disease.
3. In the case of a mutation of the RAS gene, a plausible option would be the combination of polychemotherapy and bevacizumab. The TRIBE trial describes the role of the combination of FOLFIRINOX and Bevacizumab (compared to FOLFIRI and Bevacizumab), which significantly increased the response rate between groups (53.1% vs 65.1%), although this did not correlate with higher rates resection R0.

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# Chapter 17

## Rectal Cancer



Jinhui Zhu, Kai Yu, and Ramon Andrade De Mello

**Abstract** Rectal cancer is a disease in which cancer cells form in the tissues of the rectum; colorectal cancer occurs in the colon or rectum. Adenocarcinomas comprise the vast majority (98%) of colon and rectal cancers; more rare rectal cancers include lymphoma (1.3%), carcinoid (0.4%), and sarcoma (0.3%). The incidence and epidemiology, etiology, pathogenesis, and screening recommendations are common to both colon cancer and rectal cancer.

The incidence of colorectal cancer rose dramatically following economic development and industrialization. The majority of colorectal cancers still occur in industrialized countries. Currently, the incidence of rectal cancer in the European Union is 15–25 cases/100 000 population per year and is predicted to increase further in both genders. High body mass index, body or abdominal fatness and diabetes type II are seen as risk factors. Longstanding ulcerative colitis and Crohn's disease affecting the rectum, excessive consumption of red or processed meat and tobacco as well as moderate/heavy alcohol use increase the risk.

The usual pathogenesis of colorectal cancer is an adenomatous polyp that slowly increases in size, followed by dysplasia and finally cancer. Screening for colorectal cancer is valuable because early detection and removal of premalignant adenomas or localized cancer can prevent cancer or cancer-related deaths.

Although radical resection of rectum is the mainstay of therapy, surgery alone has a high recurrence rates. A multidisciplinary approach that includes colorectal surgery, medical oncology, and radiation oncology is required for optimal treatment of patients with rectal cancer. Therefore, determination of optimal treatment plan for patients with rectal cancer involves a complex decision-making process.

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Rectal cancer recurs in 5–30% of patients, usually in the first year after surgery. Tumor stage, grade, number of lymph node metastasis, lymphovascular involvement, signet cell appearance, achievement of negative radial margins, and distance from the radial margin are important prognostic indicators of local and distant recurrences.

**Keywords** Rectal cancer · Chemotherapy · Radiotherapy

## 17.1 Introduction

Rectal cancer is a disease in which cancer cells form in the tissues of the rectum. Although the incidence of distal (rectal and lower sigmoid) cancers has declined, with a concurrent increase in more proximal colon cancers, approximately one quarter of colorectal cancers are located in the rectum. For many years, almost all patients with rectal cancer underwent abdominoperineal resection with a permanent colostomy. Today, this approach is rarely required. The successful treatment of patients with rectal cancer involves optimal surgical technique, and frequently adjuvant chemoradiotherapy. This combined modality approach will maximize cure, minimize the risk of a subsequent symptomatic local/pelvic recurrence, and maintain quality of life. Such multimodality approaches are applicable to patients with rectal cancers at or below the peritoneal reflection. This designation generally represents cancers below 12 cm from anal verger. Tumors in the upper rectum or rectosigmoid are treated by surgical resection, and adjuvant therapy is based on the colon cancer paradigm.

## 17.2 Epdimiology

Colon and rectal cancer incidence was negligible before 1900. The incidence of colorectal cancer has been rising dramatically following economic development and industrialization. Currently, the incidence of rectal cancer in the European Union is 15–25 cases/100 000 population per year and is predicted to increase further in both genders [1]. High incidences of colon and rectal cancer cases are identified in the US, Canada, Japan, parts of Europe, New Zealand, Israel, and Australia. Low colorectal cancer rates are identified in Algeria and India. The majority of colorectal cancers still occur in industrialized countries. Importantly, both colon and rectal cancer incidences, as well as mortality rates in the US, have been decreasing for the last two decades, from 66.3 per 100,000 population in 1985 to 45.5 in 2006 [2]. The rate of decrease accelerated from 1998–2006 (to 3% per year in men and 2.2% per year in women), in part because of increased screening, allowing the detection and removal of colorectal polyps before they progress to cancer. The lifetime risk of developing a colorectal malignancy is approximately 6% in the general

US population. This decrease is due to a declining incidence and improvements in both early detection and treatment.

However, in contrast to the decline in rectal cancer incidence rates in persons age 55 and older, which began in the mid-1970s, rates of rectal cancer in younger persons have been rising. From 1974 to 2013, in persons age 20–39 years, and since 1980 in adults age 30–39 years, rectal cancer incidence rates have increased 3.2% per year. In those age 40–54 years, rates have increased by 2.3% annually since the 1990s. Currently, adults born circa 1990 have quadruple the risk of rectal cancer compared with those born circa 1950 [3].

## 17.3 Etiology

The etiology of colorectal cancer is unknown, but colorectal cancer appears to be multifactorial in origin and includes environmental factors and a genetic component. Diet may have an etiologic role, especially diet with high fat content. Approximately 75% of colorectal cancers are sporadic and develop in people with no specific risk factors. The remaining 25% of cases occur in people with significant risk factors—most commonly, a family history or personal history of colorectal cancer or polyps, which are present in 15–20% of all cases. Other significant risk factors are certain genetic predispositions, such as hereditary nonpolyposis colorectal cancer (HNPCC; 4–7% of all cases) and familial adenomatous polyposis (FAP; 1%); and inflammatory bowel disease (IBD; 1% of all cases).

### 17.3.1 Environmental Factors

#### 17.3.1.1 Diet

A high-fat, low-fiber diet is implicated in the development of colorectal cancer. Specifically, people who ingest a diet high in unsaturated animal fats and highly saturated vegetable oils (eg, corn, safflower) have a higher incidence of colorectal cancer. The mechanism by which these substances are related to the development of colorectal cancer is unknown.

Saturated fats from dairy products do not have the same carcinogenic effect, nor do oils containing oleic acid (eg, olive, coconut, fish oils). Omega-3 monounsaturated fatty acids and omega-6 monounsaturated fatty acids also appear to be less carcinogenic than unsaturated or polyunsaturated fats. In fact, recent epidemiologic data suggest that high fish consumption may provide a protective effect against development of colorectal cancer. Long-term diets high in red meat or processed meats appear to increase the risk of distal colon and rectal cancers [4, 5].

The ingestion of a high-fiber diet may be protective against colorectal cancer. Fiber causes the formation of a soft, bulky stool that dilutes carcinogens; it also

decreases colonic transit time, allowing less time for harmful substances to contact the mucosa. The decreased incidence of colorectal cancer in Africans is attributed to their high-fiber, low-animal-fat diet. This favorable statistic is reversed when African people adopt a western diet. Meta-analysis of case-controlled studies found that reduction in colorectal cancer risk occurs with increasing intake of dietary fiber [4].

Increased dietary intake of calcium appears to have a protective effect on colorectal mucosa by binding with bile acids and fatty acids. The resulting calcium salts may have antiproliferative effects, decreasing crypt cell production in the mucosa. A double-blind placebo-controlled study showed a statistically significant reduction in the incidence of metachronous colorectal adenomas [6]. Other dietary components, such as selenium, carotenoids, and vitamins A, C, and E, may have protective effects by scavenging free-oxygen radicals in the colon.

### **17.3.1.2 Alcohol**

Alcohol intake of more than 30 g daily has been associated with increased risk of developing colorectal carcinoma, with risk of rectal cancer greater than that of colon cancer. Risk appears greater with beer than with wine [7]. Specifically, Kabat et al found that daily beer consumption of 32 ounces or more increases the risk of rectal cancer in men (odds ratio 3.5) [8].

### **17.3.1.3 Tobacco**

Smoking, particularly when started at a young age, increases the risk of colorectal cancer [9]. Possible mechanisms for tumor development include the production of toxic polycyclic aromatic amines and the induction of angiogenic mechanisms due to tobacco smoke. A study by Phipps et al found that smoking is also associated with increased mortality after colorectal cancer diagnosis, especially among patients with colorectal cancer with high microsatellite instability [10].

## **17.3.2 Cholecystectomy**

Following cholecystectomy, bile acids flow freely, increasing exposure to the degrading action of intestinal bacteria. This constant exposure increases the proportion of carcinogenic bile acid byproducts. A meta-analysis by Giovannucci et al revealed an increased risk of proximal colon carcinoma following cholecystectomy. Although a large number of studies suggest the increased risk of proximal colon cancer in patients following cholecystectomy, the data are not compelling enough to warrant enhanced screening in this patient population. [11]

### **17.3.3 Hereditary Factors**

The relative risk of developing colorectal cancer is increased in the first-degree relatives of affected patients. For offspring, the relative risk is 2.42 (95% CI: 2.20–2.65); when more than one family member is affected, the relative risk increases to 4.25 (95% CI: 3.01–6.08). If the first-degree family member is younger than 45 years at the time of diagnosis, the risk increase is even higher [12].

Regarding the personal history of colorectal cancer or polyps: Of patients with colorectal cancer, 30% have synchronous lesions, usually adenomatous polyps. Approximately 40–50% of patients have polyps on a follow-up **colonoscopy**. Of all patients who have adenomatous polyps discovered via a colonoscopy, 29% of them have additional polyps discovered on a repeat colonoscopy one year later. Malignancy develops in 2–5% of patients. The risk of cancer in people who have had polyps removed is 2.7–7.7 times that of the general population [13].

### **17.3.4 Genetic Disorders**

#### **17.3.4.1 Familial Adenomatous Polyposis (FAP)**

FAP is an autosomal dominant inherited syndrome that results in the development of more than 100 adenomatous polyps and a variety of extra-intestinal manifestations. The defect is in the APC gene, which is located on chromosome 5 at locus q21. The disease process causes the formation of hundreds of intestinal polyps, osteomas of bone, desmoid tumors, and, occasionally, brain tumors. Individually, these polyps are no more likely to undergo malignant transformation than are polyps in the general population. The increased number of polyps, however, predisposes patients to a greater risk of cancer. If left untreated, colorectal cancer develops in nearly 100% of these patients by age 40. Whenever the hereditary link is documented, approximately 20% of FAP cases are found to be caused by spontaneous mutation.

#### **17.3.4.2 Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**

HNPCC is an autosomal dominant inherited syndrome that occurs because of defective mismatch repair genes located on chromosomes 2, 3, and 7. Patients have the same number of polyps as the general population, but their polyps are more likely to become malignant. These patients also have a higher incidence of endometrial, gastric, thyroid, and brain cancers.

The revised Amsterdam criteria are used to select at-risk patients (all criteria must apply): (1) Three or more relatives who are diagnosed with an HNPCC-associated cancer (colorectal, endometrium, small bowel, ureter, or renal pelvis);

(2) One affected person is a first-degree relative of the other 2; (3) One or more cases of cancer are diagnosed before age 50 years; (4) At least 2 generations are affected; (5) FAP has been excluded; (6) Tumors have undergone a pathology review.

### ***17.3.5 Inflammatory Bowel Disease***

The malignant pathway in these patients does not involve any adenoma-carcinoma sequence. Cancer risk increases with duration of disease. After 10 years, the incidence of colorectal cancer in ulcerative colitis (UC) is approximately 1% per year. Patients should be evaluated for dysplastic changes via an annual colonoscopy. Dysplasia is a precursor of cancer and when present, the risk of cancer is 30%.

The incidence of colorectal cancer in patients with Crohn's disease is 4–20 times greater than that of the general population. Cancer occurs in patients with disease of at least 10 years' duration. The average age at cancer diagnosis, 46–55 years, is younger than that of the general population. Cancers often develop in areas of strictures and in de-functionalized segments of intestine. In patients with perianal Crohn's disease, malignancy is often present in fistulous tracts. Patients with Crohn's colitis should undergo the same surveillance regimen as those with UC.

## **17.4 Clinical Presentation**

All patients should undergo a complete history (including a family history) and assessment of risk factors for the development of rectal cancer. Many rectal cancers produce no symptoms and are discovered during digital or proctoscopic screening examinations.

Bleeding is the most common symptom of rectal cancer, occurring in 60% of patients. Bleeding often is attributed to other causes (eg, hemorrhoids), especially if the patient has a history of other rectal problems. Profuse bleeding and anemia are rare. Bleeding may be accompanied by the passage of mucus, which warrants further investigation.

Change in bowel habits is present in 43% of patients; change is not evident in some cases because the capacity of a rectal reservoir can mask the presence of small lesions. When change does occur it is often in the form of diarrhea, particularly if the tumor has a large villous component. These patients may have hypokalemia, as shown in laboratory studies. Some patients experience a change in the caliber of the stool. Large tumors can cause obstructive symptoms. Tumors located low in the rectum can cause a feeling of incomplete evacuation and tenesmus.

Occult bleeding is detected via a fecal occult blood test (FOBT) in 26% of all cases. Abdominal pain is present in 20% of the cases. Partial large-bowel obstruction may cause colicky abdominal pain and bloating. Back pain is usually a late sign caused by a tumor invading or compressing nerve trunks. Urinary symptoms may also occur if the tumor is invading or compressing the bladder or prostate.

Malaise is a nonspecific symptom and present in 9% of rectal cancer cases. Bowel obstruction due to a high-grade rectal lesion is rare, occurring in 9% of all cases. Pelvic pain is a late symptom, usually indicating nerve trunk involvement, and is present in 5% of all cases. Other manifestations include emergencies such as peritonitis from perforation (3%) or jaundice, which may occur with liver metastases (<1%).

## 17.5 Laboratory Studies

Routine laboratory studies should include a complete blood count (CBC); serum chemistries, including liver and renal function tests; and a carcinoembryonic antigen (CEA) test. A cancer antigen (CA) 19-9 assay, if available, may also be useful to monitor the disease.

Screening CBC may demonstrate a hypochromic, microcytic anemia, suggesting iron deficiency. The combined presence of vitamin B-12 or folate deficiency may result in a normocytic or macrocytic anemia. All men and postmenopausal women with iron deficiency anemia require a GI evaluation.

Liver function tests are usually part of the preoperative workup. The results are often normal, even in patients with metastases to the liver.

Perform a CEA test in all patients with rectal cancer. A baseline level is obtained before surgery and a follow-up level is obtained after surgery. If a previously normalized CEA begins to rise in the postoperative period, this suggests possible recurrence. A CEA level higher than 100 ng/mL usually indicates metastatic disease and warrants a thorough investigation.

Perform FOBT yearly by testing 2 samples from each of 3 consecutive stools. If any of the 6 sample findings is positive, recommend that the patient have the entire colon studied via [colonoscopy](#) or flexible sigmoidoscopy. FOBT has significant false-positive and false-negative rates.

Fecal immunochemical testing uses a monoclonal antibody assay to identify human hemoglobin. This test is more specific for lower GI tract lesions. The presence of the globin molecule is indicative of bleeding in the colon and rectum because the globin molecule is broken down during passage through the upper GI tract. This test is probably the wave of the future in fecal occult blood testing and may serve as screening in certain populations. FIT has comparable sensitivity for the detection of proximal and distal advanced neoplasia [14].



## 17.6 Screening for Colon and Rectal Cancer

The process of malignant transformation from adenoma to carcinoma takes several years. The purpose of screening is to eradicate potential cancers while they are still in the benign stage of the adenoma-carcinoma sequence. Screening also increases the likelihood of discovering existing cancers while they are still in the early stage.

Screening techniques include the following:

- Guaiac-based fecal occult blood test (FOBT): Perform FOBT yearly by testing 2 samples from each of 3 consecutive stools. If any of the 6 sample findings is positive, recommend that the patient have the entire colon studied via [colonoscopy](#) or flexible sigmoidoscopy. FOBT has significant false-positive and false-negative rates.
- Stool DNA screening (SDNA): SDNA screening is done using polymerase chain reaction of sloughed mucosal cells in stool. This test evaluates for genetic alterations that lead to the cancer formation. Compared with no testing, SDNA testing is cost effective and has high sensitivity for invasive cancer.
- Fecal immunochemical test (FIT): Fecal immunochemical testing uses a monoclonal antibody assay to identify human hemoglobin. This test is more specific for lower GI tract lesions. The presence of the globin molecule is indicative of bleeding in the colon and rectum because the globin molecule is broken down during passage through the upper GI tract. This test is probably the wave of the future in fecal occult blood testing and may serve as screening in certain populations. FIT has comparable sensitivity for the detection of proximal and distal advanced neoplasia [14].
- Rigid proctoscopy: Rigid proctosigmoidoscopy can be performed without an anesthetic, allows direct visualization of the lesion, and provides an estimation of the size of the lesion and degree of obstruction. This procedure is used to obtain biopsies of the lesion, assess ulceration, and determine the degree of fixation. The rigid proctoscopy is proven to be a highly reproducible method of determining the level of rectal cancer and does not depend on the operator and on the technique. Therefore, it gives an accurate measurement of the distance of the lesion from the anal verge; the latter is critical in deciding which operation is appropriate. The anal verge should be used as preferred landmark because the lowest edge of the rectal cancer and the anal verge can be visualized simultaneously during rigid proctoscopy evaluation. In conclusion, the level of rectal cancer must be confirmed by rigid proctoscopy [15].
- Flexible sigmoidoscopy (FSIG): Perform this test every 5 years. Biopsy any lesions identified, and perform a full colonoscopy. With flexible sigmoidoscopy, lesions beyond the reach of the sigmoidoscope may be missed. FSIG introduces significant variability for the level of rectal cancer and level of rectum itself. Therefore, FSIG should not be used to determine the level of the rectal cancer

[15]. Screening with flexible sigmoidoscopy is associated with significant decreases in the incidence of colorectal cancer (in both the distal and proximal colon) and in colorectal cancer mortality (distal colon only) [16].

- Combined glucose-based FOBT and flexible sigmoidoscopy: Theoretically, the combination of these two tests may overcome the limitations of each test.
- Double-contrast barium enema (DCBE): Although barium enema is the traditional diagnostic test for colonic polyps and cancer, the United States Preventive Services Task Force (USPSTF) did not consider barium enema in its 2008 update of colorectal cancer screening recommendations. The USPSTF noted that barium enema has substantially lower sensitivity than modern test strategies and has not been studied in trials of screening trials; its use as a screening test for colorectal cancer is declining [17].
- CT colonography (CTC): Virtual colonoscopy (CTC) was introduced in 1994. After bowel preparation, the thin-cut axial colonic images are gathered in both prone and supine positions with high-speed helical CT scanner. Then, the images are reconstituted into a 3-dimensional replica of the entire colon and rectum. This provides a good visualization of the entire colon, including the antegrade and retrograde views of the flexures and haustral folds. Because this is a diagnostic study, patients with positive findings should undergo colonoscopic evaluation the same day.
- Fiberoptic flexible colonoscopy (FFC): FFC is recommended every 5–10 years. Colonoscopy allows full visualization of the colon and excision and biopsy of any lesions. The likelihood is extremely low that a new lesion could develop and progress to malignancy between examinations.

Signs and symptoms in patients with average risk for colon and rectal cancer who should be screened include the following: (1) No symptoms and age 50–75 years; (2) No symptoms requesting screening; (3) Change in bowel habits; (4) Rectal and anal bleeding; (5) Unclear abdominal pain; (6) Unclear iron-deficiency anemia.

Each screening test has unique advantages. They have been shown to be cost-effective and have associated risks and limitations. Ultimately, patient preferences and availability of testing resources guide the selection of screening tests. The main disadvantage of the structural tests is their requirement for bowel preparation. The primary advantage of structural tests is that they can detect polyps as well as cancer. Conscious sedation is usually used for colonoscopy. FSIG is uncomfortable, and screening benefit is limited to sigmoid colon and rectum. Risks for colonoscopy, DCBE, and CTC may rarely include perforation; colonoscopy may also be associated with bleeding. Positive findings on FSIG, DCBE, and CTC usually result in referral for colonoscopy. The advantages of the stool tests are that they are noninvasive, do not require bowel preparation, and are more readily available to patients without adequate insurance coverage or local resources.

## 17.7 Histologic Findings

Histopathologic features such as poor differentiation, lymphovascular and/or perineural invasion, T4 tumor stage, and clinical findings such as obstruction or perforation, and elevated preoperative CEA levels are all associated with increased recurrence rates and worse survival [18].

## 17.8 Staging

### 17.8.1 Dukes Classification

In 1932, Cuthbert E. Dukes, a pathologist at St. Mark Hospital in England, introduced a staging system for rectal cancer. His system divided tumor classification into 3 stages, as follows:

- Those limited to the rectal wall (Dukes A);
- Those that extended through the rectal wall into extra-rectal tissue (Dukes B);
- Those with metastases to regional lymph nodes (Dukes C).

This system was modified by others to include subdivisions of stages B and C, as follows:

- Stage B was divided into B1 (ie, tumor penetration into muscularis propria) and B2 (ie, tumor penetration through muscularis propria);
- Stage C was divided into C1 (ie, tumor limited to the rectal wall with nodal involvement) and C2 (ie, tumor penetrating through the rectal wall with nodal involvement).
- Stage D was added to indicate distant metastases.

### 17.8.2 Tumor, Node, Metastasis (TNM) System

This system was introduced in 1954 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUAC). The TNM system is a universal staging system for all solid cancers that is based on clinical and pathologic information. Each category is independent. Neither the Dukes nor the TNM system includes prognostic information such as histologic grade, vascular or perineural invasion, or tumor DNA ploidy.

### 17.8.3 TNM Classification for Cancer of the Colon and Rectum (AJCC) (Table 17.1)

Primary tumor (T) includes the following:

- TX – Primary tumor cannot be assessed or depth of penetration not specified
- T0 – No evidence of primary tumor
- Tis – Carcinoma in situ (mucosal); intraepithelial or invasion of the lamina propria
- T1 – Tumor invades submucosa
- T2 – Tumor invades muscularis propria
- T3 – Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissue
- T4 – Tumor directly invades other organs or structures and/or perforates the visceral peritoneum

Regional lymph nodes (N) include the following:

- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Metastasis in 1–3 pericolic or perirectal lymph nodes
- N2 – Metastasis in 4 or more pericolic or perirectal lymph nodes
- N3 – Metastasis in any lymph node along the course of a named vascular trunk

Distant metastasis (M) include the following:

- MX – Presence of metastasis cannot be assessed
- M0 – No distant metastasis
- M1 – Distant metastasis

The TNM stage – dependent 5-year [survival rate](#) for rectal carcinomas is as follows [18]:

- Stage I – 90%
- Stage II – 60–85%
- Stage III – 27–60%
- Stage IV – 5–7%

**Table 17.1** Comparison of AJCC definition of TNM staging system to Dukes classification

Rectal Cancer Stages	TNM Staging	Dukes Staging	5-Year Survival
Stage I	T1-2 N0 M0	A	>90%
Stage II	A T3 N0 M0	B	60–85%
	B T4 N0 M0		60–85%
Stage III	A T1-2 N1 M0	C	55–60%
	B T3-4 N1 M0		35–42%
	C T1-4 N2 M0		25–27%
Stage IV	T1-4 N0-2 M1		5–7%

## 17.9 Medical Care

A multidisciplinary approach that includes surgery, medical oncology, and radiation oncology is required for optimal treatment of patients with rectal cancer.

Determination of optimal treatment plan for patients with rectal cancer involves a complex decision-making process. Strong considerations should be given to the intent of surgery, possible functional outcome, and preservation of anal continence and genitourinary functions. The timing of surgical resection is dependent on the size, location, extent, and grade of the rectal carcinoma. The number of lymph nodes removed (12 or more; minimum, 10) at the time of surgery impacts staging accuracy and prognosis. The first step involves achievement of cure because the risk of pelvic recurrence is high in patients with rectal cancer and locally recurrent rectal cancer has a poor prognosis. Functional outcome of different treatment modalities involves restoration of bowel function with acceptable anal continence and preservation of genitourinary functions. Preservation of both anal and rectal reservoir function in treatment of rectal cancer is highly preferred by patients. Sphincter-saving procedures for rectal cancer are now considered the standard of care [19].

- Factors influencing sphincter preservation: surgeon training, surgeon volume, neoadjuvant chemoradiotherapy.
- Factors associated with difficult sphincter preservation: male sex, morbid obesity, preoperative incontinence, direct involvement of anal sphincter muscles with carcinoma, bulky tumors within 5 cm from the anal verge.
- Patient selection for local excision: lesions located in low rectum (within 8–10 cm), lesions occupying less than one third of the rectal circumference, mobile exophytic or polypoid lesions, lesions less than 3 cm in size, T1 lesions, low grade tumor (well or moderately differentiated), negative nodal status (clinical and radiographic).
- Disadvantages of abdominoperineal resection: need for permanent colostomy, significantly higher short-term morbidity and mortality, significantly higher long-term morbidities, higher rate of sexual and urinary dysfunction.

## 17.10 Surgical Care

Patient-related, tumor-related, treatment-related, and surgeon-related factors influence the ability to restore intestinal continuity in patients with rectal cancer.

### 17.10.1 Transanal Excision

The local transanal excision of rectal cancer is reserved for early-stage cancers in a select group of patients. The lesions amenable for local excision are small (< 3 cm in size), occupying less than a third of a circumference of the rectum, preferably exophytic/polypoid, superficial and mobile (T1 and T2 lesions), low-grade tumors (well or moderately differentiated) that are located in low in the rectum (within 8 cm of the anal verge). There should also be no palpable or radiologic evidence of enlarged mesenteric lymph nodes. The likelihood of lymph node involvement in this type of lesion ranges from 0–12% [19, 20]. A study by Peng et al found that local excision in early stage rectal cancer may result in high local recurrence rates. The authors recommend only using this procedure in highly selective groups of patients, specifically those with a tumor size of 2.5 cm or smaller [21].

Local excision is increasingly used to treat stage I rectal cancers despite its inferiority to total mesorectal excision, which is the current standard of care. In a study of all rectal cancer patients in the National Cancer Data Base from 1998 through 2010, researchers found that local excision was used to treat 46.5% of the patients with T1 tumors and 16.8% of those with T2 tumors. For patients with T1 cancer, local excision rates increased from 39.8% in 1998 to 62.0% in 2010. For patients with T2 cancers, rates increased from 12.2% to 21.4% [22].

Preoperative ERUS should be performed. If nodes are identified as suggestive of cancer, do not perform transanal excision. The lesion is excised with the full thickness of the rectal wall, leaving a 1-cm margin of normal tissue. The defect is usually closed; however, some surgeons leave it open. Unfavorable pathologic features such as positive resection margins, lymphovascular invasion, lymph node metastasis, perineural invasions, and recurrent lesion at follow-up evaluations mandate salvage resection. Usually, an abdominal perineal resection or proctosigmoidectomy with coloanal anastomosis is performed as a salvage resection following failure of local excision [20].

The advantages of local excision include rapid recovery, minimal effect on sphincter function, and relatively low perioperative morbidity and mortality. Recovery is usually rapid. The 5-year survival rate after transanal excision ranges from 65–100% (these figures include some patients with T2 lesions). The local recurrence rate ranges from 0–40%. Patients with lesions that display unfavorable histologic features but are excised completely may be treated with adjuvant radiation therapy.

Cancer recurrence following transanal excision of early rectal cancer has been studied by Weiser et al. [23] Failures due to transanal excision are mostly advanced local disease and are not uniformly salvageable with radical pelvic excision. These patients may require extended pelvic dissection with en bloc resection of adjacent pelvic organs such as the pelvic side wall with autonomic nerves, coccyx, prostate, seminal vesicle, bladder, vagina, ureter, ovary, and uterus. The long-term outcome in patients with recurrent rectal carcinoma who undergo radical resection is less favorable than expected, relative to the early stage of their initial rectal carcinoma [23].

In summary, the treatment of T1 and T2 rectal cancers continues to be challenging. Local excision is associated with higher rate of recurrence, especially in T2 lesions. Ultimately, 15–20% of patients may experience recurrence. When local recurrence is detected, patients usually have advanced disease, requiring extensive pelvic excisions. Therefore, strict selection criteria are essential when considering local excision. All patients should be informed of the risk of local recurrence and lower cure rates associated with recurrence [19, 23, 24].

### **17.11 Endocavitary Radiation**

This radiotherapy method differs from external-beam radiation therapy in that a larger dose of radiation can be delivered to a smaller area over a shorter period. Selection criteria for this procedure are similar to those for transanal excision. The lesion can be as far as 10 cm from the anal verge and no larger than 3 cm. Endocavitary radiation is delivered via a special proctoscope and is performed in an operating room with sedation. The patient can be discharged on the same day.

A total of 6 application of high-dose (20Gy–30 Gy), low-voltage radiation (50 kV) is given over the course of 6 weeks. Each radiotherapy session produces a rapid shrinkage of the rectal cancer lesion. An additional booster dose can be given to the tumor bed. The overall survival rate is 83%, although the local recurrence rate as high as 30% [20].

### **17.12 Transanal Endoscopic Microsurgery (TEM)**

Transanal endoscopic microsurgery is another form of local excision that uses a special operating proctoscope that distends the rectum with insufflated carbon dioxide and allows the passage of dissecting instruments. This method can be used on lesions located higher in the rectum and even in the distal sigmoid colon. Transanal endoscopic microsurgery has not come into wide use yet because of a significant learning curve and a lack of availability.

### **17.13 Sphincter-Sparing Procedures**

Procedures are described that use the traditional open technique. All of these procedures, except the perineal portions, can also be performed using laparoscopic techniques, with excellent results. The nuances of the laparoscopic technique used are beyond the scope of this discussion. A study by Li et al found that laparoscopic and open surgery for middle and lower rectal cancer are associated with similar long-term outcomes. The study shows the value of technical experience when performing

laparoscopic surgery and encourages the use of this surgery by experienced teams [25]. Long-term results from the UK Medical Research Council trial of laparoscopically assisted versus open surgery for colorectal cancer showed no differences between groups in overall or disease-free survival or recurrence rates [26].

### **17.13.1 Low Anterior Resection (LAR)**

LAR is generally performed for lesions in the middle and upper third of the rectum and, occasionally, for lesions in the lower third. Because this is a major operation, patients who undergo LAR should be in good health. They should not have any preexisting sphincter problems or evidence of extensive local disease in the pelvis.

Patients will not have a permanent colostomy but should be informed that a temporary colostomy or ileostomy may be necessary. They also must be willing to accept the possibility of slightly less-than-perfect continence after surgery, although this is not usually a major problem.

Other possible disturbances in function include transient urinary dysfunction secondary to weakening of the detrusor muscle. This occurs in 3–15% of patients. Sexual dysfunction is more prominent and includes retrograde ejaculation and impotence. In the past, this has occurred in 5–70% of men, but recent reports indicate that the current incidence is lower [27].

The operation entails full mobilization of the rectum, sigmoid colon, and, usually, the splenic flexure. Mobilization of the rectum requires a technique called total mesorectal excision (TME). TME involves sharp dissection in the avascular plane that is created by the envelope that separates the entire mesorectum from the surrounding structures. This includes the anterior peritoneal reflection and Denonvilliers fascia anteriorly and preserves the inferior hypogastric plexus posteriorly and laterally. TME is performed under direct visualization. Mesorectal spread can occur by direct tumor spread, tumor extension into lymph nodes, or perineural invasion of tumor [15, 24, 27].

TME yields a lower local recurrence rate (4%) than transanal excision (20%), but it is associated with a higher rate of anastomotic leak (11%). For this reason, TME may not be necessary for lesions in the upper third of the rectum. The distal resection margin varies depending on the site of the lesion. A 2-cm margin distal to the lesion must be achieved. For the tumors of the distal rectum, less than 5 cm from the anal verge, the minimally accepted distal margin is 1 cm in the fresh specimen. Distal intra-mural spread beyond 1 cm occurs rarely. Distal spread beyond 1 cm is associated with aggressive tumor behavior or advanced tumor stage [15].

The procedure is performed with the patient in the modified lithotomy position with the buttocks slightly over the edge of the operating table to allow easy access to the rectum [24]. A circular stapling device is used to create the anastomosis. A double-stapled technique is performed. This entails transection of the rectum distal to the tumor from within the abdomen using a linear stapling device. The proximal resection margin is divided with a purse-string device.



After sizing the lumen, the detached anvil of the circular stapler is inserted into the proximal margin and secured with the purse-string suture. The circular stapler is inserted carefully into the rectum, and the central shaft is projected through or near the linear staple line. Then, the anvil is engaged with the central shaft, and, after completely closing the circular stapler, the device is fired. Two rings of staples create the anastomosis, and a circular rim or donut of tissue from the proximal and distal margins is removed with the stapling device.

According to a study by Maurer et al, the introduction of TME has resulted in an impressive reduction of local recurrence rate. TME appears to have improved survival in patients without systemic disease [28].

The anastomotic leak rate with this technique ranges from 3–11% for middle-third and upper-third anastomosis and to 20% for lower-third anastomosis. For this reason, some surgeons choose to protect the lower-third anastomosis by creating a temporary diverting stoma. This is especially important when patients have received preoperative radiation therapy. The rate of stenosis is approximately 5–20%. A hand-sewn anastomosis may be performed; if preferred, the anastomosis is performed as a single-layer technique. The leak and stenosis rates are the same.

In R0 resection, the inferior mesenteric artery (IMA) should be excised at its origin, but this rule is not mandated by available supportive evidence. Patients with non-en-bloc resection, positive radial margins, positive proximal and distal margin, residual lymph node disease, and incomplete preoperative and intra-operative staging would not be considered to have complete resection of cancer (R0 resection) [15]. Patients with R1 and R2 resection are considered to have an incomplete resection for cure. Incomplete R1 and R2 resection does not change the TNM stage but affects the curability [15]. In a 2012 multicenter, randomized controlled trial, mesorectal excision with lateral lymph node dissection was associated with a significantly longer operation time and significantly greater blood loss than mesorectal excision alone [29].

### **17.13.2 Colo-anal Anastomosis (CAA)**

Very distal rectal cancers that are located just above the sphincter occasionally can be resected without the need for a permanent colostomy. The procedure is as already described; however, the pelvic dissection is carried down to below the level of the levator ani muscles from within the abdomen. A straight-tube coloanal anastomosis (CAA) can be performed using the double-stapled technique, or a hand-sewn anastomosis can be performed transanally [27].

The functional results of this procedure have been poor in some patients, who experience increased frequency and urgency of bowel movements, as well as some incontinence to flatus and stool. An alternative to the straight-tube CAA is creation of a colonic J pouch. The pouch is created by folding a loop of colon on itself in the shape of a J. A linear stapling or cutting device is inserted into the apex of the J, and

the stapler creates an outer staple line while dividing the inner septum. The J-pouch anal anastomosis can be stapled or hand sewn.

An alternative to doing the entire dissection from within the abdomen is to begin the operation with the patient in the prone jackknife position. The perineal portion of this procedure involves an intersphincteric dissection via the anus up to the level of the levator ani muscles. After the perineal portion is complete, the patient is turned to the modified lithotomy position and the abdominal portion is performed. Either a straight-tube or colonic J-pouch anal anastomosis can be created; however, both must be hand sewn [27].

The advantages of the J pouch include decreased frequency and urgency of bowel movements because of the increased capacity of the pouch. A temporary diverting stoma is performed routinely with any coloanal anastomosis.

### 17.13.3 Abdominal Perineal Resection (APR)

APR is performed in patients with lower-third rectal cancers. APR should be performed in patients in whom negative margin resection will result in loss of anal sphincter function. This includes patients with involvement of the sphincters, preexisting significant sphincter dysfunction, or pelvic fixation, and sometimes is a matter of patient preference. (Table 17.2).

A 2-team approach is often used, with the patient in modified lithotomy position. The abdominal team mobilizes the colon and rectum, transects the colon proximally, and creates an end-sigmoid colostomy. The perineal team begins by closing the anus with a purse-string suture and making a generous elliptical incision. The incision is carried through the fat using electrocautery. The inferior rectal vessels are ligated and the anococcygeal ligament is divided. The dissection plane continues posteriorly, anterior to the coccyx to the level of the levator ani muscles.

Then, the surgeon breaks through the muscles and retrieves the specimen that has been placed in the pelvis. The specimen is brought out through the posterior opening, and the anterior dissection is continued carefully. Care must be taken to avoid the prostatic capsule in the male and the vagina in the female (unless posterior vaginectomy was planned). The specimen is removed through the perineum, and the wound is irrigated copiously. A closed-suction drain is left in place, and the perineal wound is closed in layers, using absorbable sutures. During this time, the abdominal team closes the pelvic peritoneum (this is not mandatory), closes the abdomen, and matures the colostomy [27].

**Table 17.2** Acceptable minimal distal and proximal resectional margins for rectal cancer [14]

Resection margins	Proximal resection margin (cm)	Distal resection margin (cm)
Ideal margins	5 cm or more	2 cm or more
Minimally acceptable margins	5 cm or more	1 cm or more

In patients who have rectal cancer with adjacent organ invasion, en bloc resection should be performed in order to not compromise cure. This situation is encountered in 15% of rectal cancer patients. Rectal carcinoma most commonly invades the uterus, adnexa, posterior vaginal wall, and bladder. The urinary bladder is the organ most commonly involved in locally advanced rectal carcinoma. Extended, en bloc resection may involve partial or complete cystectomy [15, 27]. In women, rectal carcinoma also commonly invades the uterus, adnexa, and posterior vaginal wall.

Inadequate sampling of lymph nodes may reflect non-oncologic resection or inadequate inspection of pathologic specimens. The use of more extended pelvic lymphadenectomy has been studied for rectal cancer. Extended lymphadenectomy involves removal of all lymph nodes along the internal iliac and common iliac arteries. This procedure has been associated with significantly higher sexual and urinary dysfunction without any additional benefit in local recurrence especially in patients with adjuvant radiotherapy [30].

### ***17.13.4 Treatment of Colorectal Cancer with Liver Metastasis***

Chemotherapeutic regimens for liver metastasis including systemic and intrahepatic administration have only had limited benefit. Systemic chemotherapy had 18–28% response rates. However, one meta-analysis found that carefully selected patients with metastatic colorectal cancer may benefit from preoperative chemotherapy with curative intent [31]. It is well accepted that liver resections in selected patients are beneficial. Overall, 5-year survival rates following surgical resection of liver metastasis vary from 20–40%. A study by Dhir et al found that among patients undergoing hepatic resection for colorectal metastasis, a negative margin of 1 cm or more had a survival advantage [32].

### **17.14 Adjuvant Medical Care**

Although radical resection of rectum is the mainstay of therapy, surgery alone has a high recurrence rates. The local recurrence rate for rectal cancers treated with surgery alone is 30–50%. Rectal adenocarcinomas are sensitive to ionizing radiation. Radiation therapy can be delivered preoperatively, intraoperatively, or postoperatively and with or without chemotherapy.

Tumor stage, grade, number of lymph node metastasis, lymphovascular involvement, signet cell appearance, achievement of negative radial margins, and distance from the radial margin are important prognostic indicators of local and distant recurrences. Low anterior (LAR) or abdominal-perineal resection (APR) in conjunctions with total mesorectal excision (TME) should be performed for optimal surgical therapy. A study by Margalit et al found that patients older than 75 years had difficulty tolerating combined modality chemotherapy to treat rectal cancer.

They required early termination of treatment, treatment interruptions, and/or dose reductions [33].

## 17.15 Adjuvant Radiation Therapy

Preoperative radiation therapy has many potential advantages, including tumor down-staging; an increase in resectability, possibly permitting the use of a sphincter-sparing procedure; and a decrease in tumor viability, which may decrease the risk of local recurrence. Preoperative radiation therapy works better in well-oxygenated tissues prior to surgery [27, 34]. Postoperatively, tissues are relatively hypoxic as a result of surgery and may be more resistant to radiotherapy. If patients have postoperative complications, there may be delay in initiating adjuvant therapy. Preoperative radiation therapy also minimizes the radiation exposure of small bowel loops due to pelvic displacement and adhesions following surgery. In a study of patients with locally advanced rectal cancer, a higher dose of radiation delivered using an endorectal boost increased major response in T3 tumors by 50% without increasing surgical complications or toxicity [35].

The disadvantages of preoperative radiation therapy include delay in definitive resection, possible loss of accurate pathologic staging, possible over-treatment of early-stage (stage I and II) rectal cancer, and increased postoperative complications and morbidity and mortality rates secondary to radiation injury. Preoperative radiation therapy decreases the risk of tumor recurrence in patients with stage II or III disease; however, this does not translate into a decrease in distant metastases or an increase in survival rate. Some recent reports cite an increase in survival; however, this is still the minority opinion.

In sum, preoperative radiotherapy may be effective in improving local control in localized rectal cancer but is only of marginal benefit in attainment of improved overall survival; it does not diminish the need for permanent colostomies and it may increase the incidence of postoperative surgical infections; it also does not decrease the incidence of long-term effects on rectal and sexual function [36]. The authors recommend preoperative chemoradiation therapy in patients with large bulky cancers and with obvious nodal involvement [27].

The advantages of postoperative radiation therapy include immediate definitive resection and accurate pathologic staging information before beginning ionizing radiation. The disadvantages of postoperative radiation therapy include possible delay in adjuvant radiation therapy if postoperative complications ensue; no effect on tumor cell spread at the time of surgery; and decreased effect of radiation in tissues with surgically-induced hypoxia. Published randomized trials suggest that preoperative or postoperative radiation therapy appears to have a significant impact on local recurrence but does not increase survival rates [27]. A study by Ng et al found that statin use during and after adjuvant chemotherapy did not result in improved disease-free survival, recurrence-free survival, or overall survival in patients with stage III colon cancer [37].

### ***17.15.1 Intraoperative Radiation Therapy***

Intraoperative radiation therapy is recommended in patients with large, bulky, fixed, unresectable cancers. The direct delivery of high-dose radiotherapy is believed to improve local disease control. Intraoperative radiation therapy requires specialized, expensive operating room equipment, limiting its use.

### ***17.15.2 Adjuvant Chemotherapy***

Chemotherapy options for colon and rectal cancer have greatly expanded in recent years, but the efficacy of chemotherapy remains incomplete and its toxicities remain substantial. Combination therapy with use of as many drugs as possible is needed for maximal effect against rectal cancer. (Table 17.3).

The most useful chemotherapeutic agent for colorectal carcinoma is 5-fluorouracil (5-FU), an antimetabolite. The prodrug, 2-deoxy-5-fluoruridine (5-FUDR), is rapidly converted to 5-FU and is used for metastatic liver disease by continuous intrahepatic infusion. Fluorouracil is a fluorinated pyrimidine, which blocks the formation of thymidylic acid and DNA synthesis. Clinically, it offers good radiosensitization without severe side effects, although diarrhea can be dose limiting and, if severe, life-threatening. 5-FU has been used in conjunction with radiation (combined modality) therapy before surgery (neoadjuvant), as well as after surgery.

Stage I (T1-2, N0, M0) rectal cancer patients do not require adjuvant therapy due to their high cure rate with surgical resection. High-risk patients, including those with poorly differentiated tumor histology and those with lymphovascular invasion, should be considered for adjuvant chemotherapy and radiotherapy. The new [NCCN guidelines](#) recommend combination therapy with infusional fluorouracil, folinic acid, and oxaliplatin (FOLFOX) as reasonable for patients with high-risk or intermediate-risk stage II disease; however, FOLFOX is not indicated for good- or average-risk stage II rectal cancer [38, 39]. FOLFOX is associated with neuropathy and one long-term study confirmed that although overall neurotoxicity did not significantly increase after a median of 7 years, specific neurotoxicity (numbness and tingling of the hands and feet) remained elevated [40].

Patients with locally advanced rectal cancer (T3-4, N0, M0 or Tany, N1-2, M0) should receive primary chemotherapy and radiotherapy. The combination of preoperative radiation therapy and chemotherapy with fluorouracil improves local control, distant spread, and survival. The basis of this improvement is believed to be the activity of fluorouracil as a radiosensitizer. Surgical resection can be done 4–10 weeks after completion of chemotherapy and radiotherapy.

A study by Kim et al found that postoperative complications were associated with both omission of and delay in chemotherapy. Timely initiation of chemotherapy, defined as before 8 weeks postoperatively, was a factorable prognostic factor for overall and recurrence-free survival [41].

**Table 17.3** Colorectal chemotherapeutic regimens

Colon and rectal cancer common chemotherapy regimens	
FOLFOX (Every 2 weeks)	Oxaliplatin 85 mg/m <sup>2</sup> day 1
	Leucovorin 200 mg/m <sup>2</sup> day 1
	5-FU 400 mg/m <sup>2</sup> IV Bolus day 1 and 2
	5-FU 600 mg/m <sup>2</sup> IV Infusion day 1 and 2 (22 h)
FOLFOX 4 (Every 2 weeks) (4 cycles)	Oxaliplatin 85 mg/m <sup>2</sup> day 1
	Leucovorin 200 mg/m <sup>2</sup> day 1
	5-FU 400 mg/m <sup>2</sup> IV Bolus day 1 and 2
	5-FU 2400 mg/m <sup>2</sup> IV Infusion day 1 (46 h)
mFOLFOX 6 (Every 2 weeks) (4 cycles)	Oxaliplatin 85 mg/m <sup>2</sup> day 1
	Leucovorin 400 mg/m <sup>2</sup> day 1
	5-FU 400 mg/m <sup>2</sup> IV Bolus day 1 and 2
	5-FU 1200 mg/m <sup>2</sup> IV Infusion day 2 days
CapeOX (Twice daily × 14 days) (Every 3 weeks)	Oxaliplatin 130 mg/m <sup>2</sup> day 1
	Capecitabine 850 mg/m <sup>2</sup> PO BID for 14 days
FOLFIRI (Every 2 weeks)	Irinotecan 165 mg/m <sup>2</sup> day 1
	Leucovorin 200 mg/m <sup>2</sup> day 1
	5-FU 400 mg/m <sup>2</sup> IV Bolus day 1 and 2
	5-FU 600 mg/m <sup>2</sup> IV Infusion day 1 and 2 (22 h)
FOLFOXIRI (Every 2 weeks)	Irinotecan 180 mg/m <sup>2</sup> day 1
	Oxaliplatin 85 mg/m <sup>2</sup> day 1
	Leucovorin 200 mg/m <sup>2</sup> day 1
	5-FU 3200 mg/m <sup>2</sup> IV Infusion day (48 h)
Bevacizumab	5–10 mg/kg IV every 2 weeks with chemotherapy
Cetuximab	400 mg/m <sup>2</sup> IV day 1, then 250 mg/m <sup>2</sup> IV weekly

Use of FOLFOX or the combination of folinic acid, fluorouracil, and irinotecan (FOLFIRI) is recommended in treatment of patients with stage III or IV disease.

### 17.15.3 Adjuvant Chemoradiation Therapy

In patients with resectable stage II and III resectable rectal cancer, preoperative chemoradiation enhances the pathological response and improves local control; however, it does not improve either disease-free or overall survival [42]. A study by Ebert et al of colorectal cancer genetics and treatment found a link between hypermethylation of transcription factor AP-2 epsilon (TFAP2E) and clinical nonresponsiveness to chemotherapy in colorectal cancer [43].

### **17.15.4 Radioembolization**

A prospective, multicenter, randomized phase III study by Hendlisz et al compared the addition of yttrium-90 resin to a treatment regimen of fluorouracil 300 mg/m<sup>2</sup> IV infusion (days 1–14 q8wk) with fluorouracil IV alone. Yttrium-90 was injected intra-arterially into the hepatic artery. Findings showed that the addition of radioembolization with yttrium-90 significantly improved time to liver progression and median time to tumor progression [44].

### **17.16 Prevention**

On December 22, 2010, the US Food and Drug Administration approved the use of quadrivalent human papilloma virus (HPV) vaccine (Gardasil) for prevention of anal cancer and associated precancerous lesions in people aged 9–26 years. HPV is associated with about 90% of anal cancer. In a study of homosexual males, HPV vaccine was shown to be 78% effective in prevention of HPV 16- and 18-related anal intraepithelial neoplasms.

### **17.17 Prognosis**

Overall 5-year survival rates for rectal cancer are as follows:

- Stage I, 90%
- Stage II, 60% to 85%
- Stage III, 27% to 60%
- Stage IV, 5% to 7%

Fifty percent of patients develop recurrence, which may be local, distant, or both. Local recurrence is more common in rectal cancer than in colon cancer.

- Disease recurs in 5–30% of patients, usually in the first year after surgery.
- Factors that influence the development of recurrence include surgeon variability, grade and stage of the primary tumor, location of the primary tumor, and ability to obtain negative margins.
- Surgical therapy may be attempted for recurrence and includes pelvic exenteration or APR in patients who had a sphincter-sparing procedure.
- Radiation therapy generally is used as palliative treatment in patients who have locally unresectable disease.

## Questions & Answers

### 1. Why Is Colorectal Cancer Increasing in Younger Patients?

Colorectal cancer (CRC) has long been considered an older person's disease. But a new American Cancer Society (ACS) report challenges that notion with findings that point to a dramatic rise in CRC among younger individuals.

Three in 10 CRC diagnoses now occur among people younger than 55 years, the report found, and rates among young and middle-aged adults have returned to what they were for people born around 1890. Someone born in 1990 now has double the risk for colon cancer and quadruple the risk for rectal cancer compared with someone born around 1950, lead author, Rebecca Siegel, MPH, from the ACS in Atlanta, Georgia, told Medscape Medical News in a recent interview.

Most experts don't advise CRC screening for average-risk individuals until age 50, so diagnosis of younger adults is often not on clinicians' radar. The report didn't explore the reason for the sharp increase of the condition in people under 50, but the authors speculate that it might be related to obesity, sedentary lifestyle, and lack of access to healthcare, which is often associated with later diagnosis and worse prognosis.

### 2. Is laparoscopic surgery superior, inferior, or equal to open surgery for management of patients with rectal cancer?

There is considerable controversy about the best surgical operative method for management of lower bowel cancer. It seems reasonable that in this anatomic region with limited visibility, a laparoscopic approach would allow for more complete tumor removal.

However, in the summary results from combining available published reports of randomized trials, the current overall results suggest that noncomplete tissue excision is increased by about 30% in patients undergoing laparoscopic surgery.

Is this the final word on the topic? Not at all. Surgeons need to wait until comparative randomized trials with long-term survival data are available.

### 3. In patients with rectal cancer who have had a diverting ileostomy, is early closure of the ileostomy beneficial?

In a recent randomized trial published in *Annals of Surgery*, the authors compared 55 patients allocated to an early closure group (8–13 days after stoma creation) with 57 patients in a late closure group (> 12 weeks). After 1 year of follow-up, an average of 1.2 complications per patients occurred in the early closure group compared with 2.9 complications per patient in the delayed closure group ( $P < .001$ ).

Many studies have confirmed that diverting fecal flow after a low anterior resection is a beneficial procedure. However, there may be various complications associated with the diverting procedure, and these complications may be related to the duration of the ileostomy.



This randomized trial carried out in several Scandinavian centers found that early closure of the diverting ileostomy significantly reduced the total number of complications. Furthermore, early closure of the ileostomy minimized many troublesome but nonfatal complications, such as skin irritation, ulceration, and leakage, associated with the ileostomy.

As the authors point out, one potential study weakness is that only about one third of the 418 potentially available patients were eventually included in the final analysis. Nevertheless, the findings imply that for many patients, closing a diverting ileostomy soon after the original rectal excision is beneficial as well as safe.

#### **4. Is ‘Watch-and-Wait’ Safe in Selected Rectal Cancer Patients?**

New data support the “watch-and-wait” side of the ongoing debate about the best approach to treatment for patients with rectal cancer. With improved survival now being seen after initial chemoradiation, some experts are arguing for omitting surgery in lieu of observation.

In the largest patient series to date in which surgery was omitted after induction therapy, the authors found that 3-year survival was 91%, which is similar to historic survival rates among patients who receive surgery.

For patients who experienced local recurrence, the 3-year survival was 87%.

#### **5. Is Total Neoadjuvant Approach Promising in Locally Advanced Rectal Cancer?**

Preoperative chemotherapy in combination with chemoradiation (total neoadjuvant therapy, or TNT) appears to have advantages over traditional approaches to treating locally advanced rectal cancer, according to new research.

TNT has been developed to optimize delivery of effective systemic therapy aimed at micrometastases, Dr. Martin R. Weiser of Memorial Sloan Kettering Cancer Center, in New York City, and colleagues note in *JAMA Oncology*.

#### **6. Is Radical Surgery Needed in Rectal Cancer for All Patients?**

Do patients with rectal cancer who have responded optimally to chemoradiation need to undergo surgery as well? The answer to that is up for grabs, with strong viewpoints on both sides of the coin.

Experts arguing against surgery are urging that patients can be followed with “a wait and see” approach, but experts for surgery argue that this places patients at unnecessary risk for relapse.

The two sides of this debate are outlined in a pair of articles published online in the December 22 in *JAMA Oncology*. In the article, Heidi Nelson, MD, Nikolaos Machairas, MD, and Axel Grothey, MD, all from the Mayo Clinic, Rochester, Minnesota, argue that The curative contribution of surgery is substantial. However, Other institutions, the authors note, have reported the evidence that some patients do not need to undergo a radical resection is frankly undeniable. The ideal would be to compare watch and wait with standard total mesorectal excision in a randomized

clinical trial with clear long-term oncologic and functional outcome measures. But such a trial seems unlikely, the authors point out, considering the morbidity and mortality associated with the surgical procedure and the comparable oncologic and survival outcomes that have already been reported with observation.

### **7. Obesity Linked to Increased Cancer Frequency in Young Adults.**

Cancer in adults younger than 50 years is occurring with more frequency. The increase may be due to obesity, according to a new study. As overweight and obesity have become a major public health problem almost everywhere around the globe, cancer in young adults is also increasing. Obesity is associated not only with an increase in the incidence of certain cancers but also with a worse prognosis for patients with cancer who are obese. In addition to its association with an increase in the incidence of cancer and worse prognoses, obesity hastens the development of cancer.

### **8. Does Intensive Surveillance After Colorectal Cancer Surgery Improve Outcomes?**

Outcomes after colorectal-cancer surgery are no better with more- versus less-intensive surveillance, according to two new studies in the May 22/29 issue of JAMA. Five-year overall mortality did not differ significantly between high-frequency (13.0%) and low-frequency follow-up (14.1%), the researchers report. Similarly, there were no significant differences between the groups in five-year colorectal-cancer-specific mortality rates (10.6% vs. 11.4%, respectively) or in risk of colorectal-cancer-specific recurrence (21.6% vs. 19.4%, respectively).

### **9. Total Mesorectal Excision**

Total mesorectal excision (TME) is a common procedure used in the treatment of colorectal cancer in which a significant length of the bowel around the tumor is removed. TME addresses earlier treatment concerns regarding adequate local control of rectal cancer when an anterior resection is performed. TME is indicated as a part of low anterior resection for patients with adenocarcinoma of the middle and lower rectum. It is now considered the gold standard for tumors of the middle and the lower rectum. TME is indicated as a part of low anterior resection for patients with adenocarcinoma of the middle and lower rectum. It is now considered the gold standard for tumors of the middle and the lower rectum.

### **10. Early Colorectal Cancer: Missing the Clues?**

Colorectal cancer (CRC) is up significantly in those under age 50, and the increase of CRC in young adults in their 20s and 30s is alarming. Early detection is where the primary care doctor plays a critical role. When CRC-like symptoms are present, regardless of a patient's age, it is important not to dismiss them or chalk them up to more benign causes simply because the patient is under 50, 30, or, sadly, even under 20.

### **11. To Drain or Not to Drain Infraperitoneal Anastomosis After Rectal Excision for Cancer.**

In a recent randomized trial published in *Annals of Surgery*, the authors compared 236 with drain and 233 without. The rate of pelvic sepsis, reoperation, and rate of stoma closure was similar between drain and no drain. This randomized trial suggests that the use of a pelvic drain after rectal excision for rectal cancer did not confer any benefit to the patient.

### **12. Definitions of High and Low Risk With Help of MRI**

The German investigators used MRI to help differentiate high and low risk. Preoperative MRI can determine the relationship between the tumour and the mesorectal fascia (the potential resection margin). MRI done before therapy “should enable distinction between patients at low risk of LR [local recurrence] (uninvolved mrCRM that does not need preoperative CRT) and patients at high risk (involved mrCRM that requires preoperative CRT to downstage the tumour for a negative pCRM resection).”

### **13. Improved Rectal-Cancer Survival Seen With Adjuvant Chemotherapy.**

Adjuvant chemotherapy is associated with improved overall survival in patients with rectal cancer and pathological complete response after neoadjuvant chemotherapy and resection, according to results from two studies of the National Cancer Database (NCDB).

### **14. Colorectal Cancers on the Rise in Younger Adults.**

Expert don't know why the rates of colorectal cancer are rising among young people. a third of the cases can be attributed either to a genetic condition or family history of the disease. For the remaining two-thirds, it's unclear. Changes in diet over the last few decades as a possible explanation, Younger people today eat a lot more fast food and processed food – things we know are associated with colorectal and other kinds of cancers. Hormones and antibiotics used on livestock and found in meat and other animal products might reduce the ability of our gut bacteria to protect us from disease. There's a lot of speculation about potential underlying causes.

### **15. Indications for Screening in Patients at high Risk for Colon and Rectal cancer.**

A patient's family history or personal history may indicate increased risk for colorectal cancer. Patients at high risk for colon and rectal cancer due to family history who should be included in surveillance programs include those with the following: Family history of colon and rectal cancer; First-degree relative with adenoma aged younger than 60 years; Genetic cancer syndromes; Hereditary nonpolyposis colorectal cancer (HNPCC); Familial adenomatous polyposis (FAP).

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# Chapter 18

## Anal Cancer



**Tiago Costa de Pádua, Hakaru Tadokoro, Ramon Andrade De Mello, and Nora Manoukian Forones**

**Abstract** Anal cancer is a rare malignancy, with increasing incidence, strongly associated with HPV infection. After making the diagnosis, a multidisciplinary discussion is essential for better management. The cornerstone of the treatment is chemoradiotherapy for localized disease with good chances of cure and preservation of the anal function. In cases of relapsed or metastatic disease, systemic therapy is indicated. There is a lack of randomized trials and prognosis is still poor. Immunotherapy represents a hope in the treatment of this disease.

**Keywords** Anal cancer · HPV infection · Chemoradiotherapy · Immunotherapy

### Abbreviations

SCC	Squamous cell carcinoma
HPV	Human papillomavirus
MSM	Men who have sex with other man
HIV	Human immunodeficiency virus

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AIN	Anal squamous intra-epithelial lesions
DRE	Digital rectal examination
MRI	Magnetic resonance imaging
EUS	Endoanal ultrasound
CT	Computed tomography
PET/CT	Positron emission tomography
TNM	Tumor–node–metastasis
AJCC	American Joint Committee on Cancer
UICC	Union for International Cancer Control
CRT	Chemoradiotherapy
IMRT	Intensity-modulated radiation therapy

## 18.1 Introduction

Anal cancer is an uncommon malignancy originated in the most distal part of the digestive system. The majority of cases are squamous cell carcinoma (SCC), but other histologic types of malignancy can arise in the anal canal, including adenocarcinoma, melanoma and rarely sarcoma [1]. This chapter will review clinical features, diagnosis and management of SCC.

## 18.2 Epidemiology and Incidence

Compared to other types of cancer, anal cancer is a rare malignancy. Despite the rarity, incidence is increasing over the last 30 years probably secondary to infection with human papillomavirus (HPV), especially in men who have sex with other man (MSM) and human immunodeficiency virus (HIV) infected patients.

In Europe, approximately 4300 patients are diagnosed with anal cancer every year [2] and in Unites States (US) represents 2.5% of all digestive system cancer, with more than 8000 expected new cases in 2017 [3]. This type of cancer is more prevalent in women than men and the median age at diagnosis is about 60 years. More than 90% of all cases are associated with HPV infection, especially HPV type 16.

### 18.2.1 Risk Factors

There are multiple recognized risk factors associated with the anal cancer, including:

- HPV infection
- HIV infection
- Post organ transplant patients (Chronic immunosuppression) [4]
- Chronic corticoid therapy for the treatment of autoimmune disease

- Promiscuous sexual behavior
- Multiple sexual partners
- Receptive anal intercourse
- Female gender
- History of cervical, vulvar, or vaginal carcinoma
- Cigarette smoking [5]
- Crohn's disease

### 18.3 Molecular Mechanisms

The molecular mechanisms involved in anal cancer pathogenesis are complex and recent studies showed strongly association with HPV infection. Anal squamous intraepithelial lesions (AIN) represent precancerous lesions and the progression to anal cancer is associated with immunosuppression, HIV infection and HPV infection.

Mutations in the APC, p53 and DCC tumor suppressor genes represent some possible alterations related to anal cancer. In HIV patients one possible mechanism is microsatellite instability [6].

### 18.4 Clinical Manifestations

The clinical manifestations of anal cancer are generally late and in the majority of patients the first symptom is rectal bleeding (45%) that is commonly attributed to hemorrhoids. Other frequent symptoms include anorectal pain (30%), palpable mass, non-healing ulcer and fecal incontinence but up to 20% of patients have no symptoms at diagnosis. Lymphadenopathy is not frequent but can occur in advanced stages [7, 8].

### 18.5 Diagnosis and Staging

Clinical assessment is the first step and includes complete anamneses, physical exam and digital rectal examination (DRE). Diagnosis is made by biopsy guided by proctoscopy to confirm the histology. For Local staging is recommended magnetic resonance imaging (MRI) or endoanal ultrasound (EUS). To assess distant metastasis, computed tomography (CT) of the thorax and abdomen can be done, but Positron emission tomography (PET)/CT should be performed when available due to high sensitivity to detect positive lymph nodes. PAAF of inguinal nodes is indicated in case of clinical suspicion

The most common staging system is the tumor–node–metastasis (TNM) established by The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) [9]. More than 50–60% of patients are



**Table 18.1** TNM staging

<b>T-tumor size</b>	
TX	Primary tumor not assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion
T1	Tumor $\leq 2$ cm
T2	Tumor $> 2$ cm but $\leq 5$ cm
T3	Tumor $> 5$ cm
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder
<b>N-nodes</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes
<b>M-metastasis</b>	
M0	No distant metastasis
M1	Distant metastasis

diagnosed with T1 or T2 lesions and the probability of nodal involvement is directly associated to tumor location and size [8] (Table 18.1).

## 18.6 Pathology

Anal canal extends from anorectal junction to anal verge and is divided by the dentate line, which represents the transition of squamous mucosa to glandular or transitional mucosa. Different histologic types of anal cancer can occur in this area and in the past they were classified as keratinizing or nonkeratinizing according to their position to dentate line, but this terminology is no longer used in clinical practice because there is no proven prognostic implication. Tumors originated in squamous or transitional mucosa are classified as squamous cell cancer, which is the most frequent type. Adenocarcinoma arising in this area is a rare condition and behaves as rectal cancer [10].

## 18.7 Treatment Approaches

Historically the treatment of anal cancer was based on surgery with abdominoperineal resection but it was associated with high morbidity and high rates of recurrence [11]. In 1974, a small study by Nigro et al [12] suggested exciting outcomes when

radiotherapy was combined with chemotherapy, and after more than 40 years this treatment is still the standard of care in anal cancer.

### 18.7.1 *Locoregional Therapy*

Concurrent chemoradiotherapy (CRT) is the standard of care for the treatment of anal cancer, and is based in the Nigro regimen, which consists of radiotherapy associated with infusional chemotherapy (fluorouracil plus mitomycin) and results in more than 80% of pathologic complete response and approximately 15% of local recurrence [12]. Other trials tested the same regimen with small changes and confirmed the benefits [13].

In attempt to reduce toxicity and improve outcomes, randomized studies tested cisplatin instead of mitomycin but with no improvement in outcomes and similar overall toxicity [14]. This combination represents an alternative, especially when mitomycin is not available. Other trials attempted to use neoadjuvant or maintenance chemotherapy before or after CRT but the outcome demonstrated was not positive and these practices were abandoned. Other tested strategy was the association of cetuximab, an anti-*EGFR* monoclonal antibody, with CRT but toxicity was excessive which cause this drug not to be used in the treatment of anal cancer. A phase II trial evaluating capecitabine instead of infusional 5-FU, demonstrated good outcomes with minimal toxicity and represents a more convenient alternative [15].

The recommended dose of radiotherapy is 45–50 Gy to the primary tumor and the fields should include anal canal and inguinal lymph nodes. For advanced tumors (T3 or T4) an additional boost should be considered [16]. When available, intensity-modulated radiation therapy (IMRT) is the preferred technique as it provides reduced toxicity and, at least, similar outcomes were demonstrated in studies [17].

The optimal time for assessment of response after CRT is controversial and studies suggested ongoing responses until week 26 [18]. Guidelines from NCCN and ESMO recommend first evaluation at week 8–12 using DRE and radiological exams [2, 16]. Expectant management is indicated until week 26 and if there is a suspicion of persistent disease, a biopsy should be performed. Salvage surgery is indicated in case of positive biopsy.

Other indication for surgical management is local recurrence. Besides the high morbidity, abdominoperineal resection is the procedure of choice and can provide long-term disease control in almost 50% of patients with isolated local recurrence [19].

SCC localized at anal margin should be treated as anal canal cancer, with exception to T1 (<2 cm), N0 well-differentiated lesions, when local excision with free margins represents an option. In case of positive margins, re-excision or CRT is indicated.

In regards to the treatment of anal cancer in HIV patients, studies suggest that the prognosis is similar when compared to non-infected patients [20] and the treatment in this population should follow general guidelines with caution in relation to toxicity. In some patients, dose adjustment or no use of mitomycin should be considered (Table 18.2).

**Table 18.2** Protocols for treatment (CRT)

Regimen- Drugs	Dosage	Days of application
Mitomycin	10 mg/m <sup>2</sup> IV (dose maximum: 20 mg)	D1 and D29
+		
5-FU [13, 14]	1000 mg/m <sup>2</sup> per day IV	D1-D4 and D29- D32
Mitomycin	10 mg/m <sup>2</sup> IV (dose maximum: 20 mg)	D1
+		
Capecitabine [22]	1650 mg/m <sup>2</sup> per day	On radiation days
Cisplatin	75 mg/m <sup>2</sup> IV	D1 and D29
+		
5-FU [23]	1000 mg/m <sup>2</sup> per day IV	D1-D4 and D29- D32

Mitomycin dose on D29 can be omitted in attempt to reduce toxicity [21]

**Table 18.3** Protocols for advanced/ metastatic disease

Regimen- Drugs	Dosage	Days of application
Cisplatin	75 mg/m <sup>2</sup> IV	D1 q4w
+		
5-FU [22]	1000 mg/m <sup>2</sup> per day IV	D1-D4 q4w
Carboplatin	AUC 6	D1 q3w
+		
Paclitaxel [23]	200 mg/m <sup>2</sup>	D1 q3w

### 18.7.2 Advanced Disease (Systemic Therapy)

The most common sites of metastasis are liver and lungs but less than 20% of patients relapse with distant metastasis. The major concern is about local recurrence, especially when salvage surgery is not feasible. The prognosis in these cases is poor and systemic therapy is indicated. There is a paucity of randomized trials evaluating the best regimen for metastatic anal cancer and there is no standard protocol. Cisplatin plus 5-FU represents the most used protocol but other drugs as carboplatin and taxanes can be used according to performance status of the patient, renal function and previous protocols used for CRT. All patients should be included in palliative care for palliation of pain and other possible symptoms (Table 18.3).

### 18.7.3 Future Developments

Immunotherapy for anal cancer was evaluated in phase II trials using nivolumab or pembrolizumab with encouraging disease control rate and description of complete responses [24, 25]. Nowadays there is no approval for immunotherapy but there are ongoing trials and represents hope in the treatment of this rare disease with limited therapeutic options.

**Key Points**

- Anal cancer is a rare condition but with increasing incidence
- HPV infection and smoking are the main risk factors
- The diagnosis is generally late and anal bleeding is the most common symptom
- Multidisciplinary discussion is essential for decision of treatment
- Chemoradiotherapy is the standard of care for localized disease and surgery is reserved for salvage in cases of recurrence
- Systemic therapy is indicated for advanced or metastatic disease
- Immunotherapy represents hope

**Clinical Case**

A 57-year-old woman with no significant past medical history presented for an appointment complaining of intermittent rectal bleeding with no improvement with measures for hemorrhoids disease. Digital rectal examination showed a 14-mm nodule in the anal canal. Proctoscopy with biopsy of the lesion close to dentate line was performed and pathology was positive for squamous cell carcinoma. EUS and PET-CT showed localized disease with no distant metastasis or lymph nodes involvement. The case was discussed in a multidisciplinary discussion and was indicated chemoradiotherapy, using IMRT technique and 5-FU plus mitomycin as chemotherapy protocol. Treatment was well tolerated and was delivered with no interruption. Two years later, routine CTs showed multiple liver nodules suspicious for metastasis. Biopsy confirmed distant recurrence and systemic therapy was initiated with Cisplatin plus 5-FU. Besides initial response, progression of disease was observed after 6 months of chemotherapy and the patient was enrolled in an immunotherapy clinical trial.

**Multiple-Choice Questions**

1. Which is the most common histologic type of anal cancer?
  - (a) Squamous cell carcinoma (SCC)
  - (b) Adenocarcinoma
  - (c) Melanoma
  - (d) Sarcoma
  - (e) Neuroendocrine carcinoma

The correct answer is (a). The majority of cases are squamous cell carcinoma (SCC), but other histologic types of malignancy arise in the anus, including adenocarcinoma, melanoma, and rarely, sarcoma.

2. Choose the correct alternative:
  - (a) The incidence of anal cancer is decreasing over the last 30 years
  - (b) The incidence of anal cancer in Unites States represents more than 5% of all digestive system cancer.
  - (c) This type of cancer is more prevalent in men than women
  - (d) The median age at diagnosis is about 40 years.
  - (e) More than 90% of all cases are associated with HPV infection, especially HPV type 16.

The correct answer is (e). The incidence of anal cancer is increasing over the last 30 years and represents approximately 2.5% of digestive cancer in US. It is more common in women and the median age at diagnosis is 60 years.

3. All options above represent risk factors for anal cancer, with exception of:
- (a) Smoking cigarette
  - (b) HPV infection
  - (c) HIV infection
  - (d) Chronic immunosuppression
  - (e) Male Gender

The correct answer is (e). Female gender represents a risk factor for anal cancer. The incidence in women is greater than in men.

4. Choose among the option above the possible molecular mechanisms associated with the pathogenesis of anal cancer in HIV patients:
- (a) Mutations in the APC tumor suppressor genes
  - (b) Mutations in p53 tumor suppressor genes
  - (c) Mutations in DCC tumor suppressor genes
  - (d) Microsatellite instability

The correct answer is (d). Mutations in the APC, p53 and DCC tumor suppressor genes represent some possible alteration related to anal cancer. In HIV infected-patients one possible mechanism is microsatellite instability

5. Choose the most common symptom presented at diagnosis of anal cancer:
- (a) Anorectal pain
  - (b) Palpable mass
  - (c) Rectal bleeding
  - (d) Non-healing ulcer
  - (e) Fecal incontinence

The correct answer is (c). Rectal bleeding is the most common symptom and generally is attributed to hemorrhoids. Lymphadenopathy can occur in advanced stages.

6. Choose the false alternative about the diagnosis and staging of anal cancer:
- (a) PAAF of inguinal nodes is always indicated to detect lymph node involvement
  - (b) For Local staging is recommended magnetic resonance imaging (MRI) or endoanal ultrasound (EUS)
  - (c) Computed tomography (CT) of the thorax and abdomen are recommended to assess distant metastasis
  - (d) Positron emission tomography (PET)/CT is an option with high sensitivity to detect involved lymph nodes.

The answer is (a). PAAF is indicated just in case of clinical suspicion.

7. Choose the false alternative for the TNM staging of anal cancer:

- (a) Invasion of vagina represent a T3 lesion
- (b) Invasion of bladder represent a T4 lesion
- (c) Metastasis in external iliac lymph nodes represent a N1b lesion
- (d) M1 indicates distant metastasis

The correct answer is (a). Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder, are classified as a T4 lesion

8. Choose the chemotherapy regimen used in the Nigro Protocol:

- (a) Capecitabine plus mitomycin
- (b) Cisplatin plus 5-FU
- (c) Cisplatin plus capecitabine
- (d) Mitomycin plus 5-FU

The correct answer is (d). Concurrent chemoradiotherapy (CRT) is the standard of care for the treatment of anal cancer, and is based in the Nigro regimen, which consists of radiotherapy associated with infusional chemotherapy (fluorouracil plus mitomycin)

9. Choose the false alternative of assessment of response after CRT in anal cancer:

- (a) The optimal time to assess response after CRT is controversial.
- (b) ESMO and NCCN guideline recommend first assessment at week 12 and expectant management until week 26
- (c) Ongoing responses are possible until week 26
- (d) If there is a suspicion of persistent disease, there is no need of a biopsy

The correct answer is (d). Expectant management is indicated until week 26 and if there is a suspicion of persistent disease, a biopsy should be performed. Salvage surgery is indicated in case of positive biopsy.

10. A 57-year-old woman with no significant past medical history presented for an appointment complaining of intermittent rectal bleeding with no improvement with measures for hemorrhoids disease. Digital rectal examination showed a 14-mm nodule in the anal canal. Choose the next step:

- (a) MRI
- (b) Colonoscopy
- (c) Proctoscopy with biopsy
- (d) Surgery

The correct answer is (c). Diagnosis is made by biopsy guided by proctoscopy to confirm the histology.

11. About the case clinic presented in question 10, EUS and PET-CT showed localized disease with no distant metastasis or lymph nodes involvement. Which is the treatment of choice:

- (a) Surgery
- (b) Definitive chemoradiotherapy
- (c) Induction chemotherapy
- (d) Palliative chemotherapy

The correct answer is (b). Concurrent chemoradiotherapy (CRT) is the standard of care for the treatment of anal cancer, and is based in the Nigro regimen, which consists of radiotherapy associated with infusional chemotherapy (fluorouracil plus mitomycin).

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# Chapter 19

## Small Intestine Cancer



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**Abstract** Primary small intestine cancers are not frequent, accounting for <1% of all adult neoplasms. Various histologic types are associated with small intestine cancer. The most common used to be adenocarcinoma; however, carcinoid tumors are showing an improved incidence and are the most common histologic type in some series. Adenocarcinomas are more frequent in the duodenum, while carcinoid tumors are more common in the ileum. Other histologic types are lymphomas and sarcomas. The symptoms are vague and non-specific. Less of an index of suspicious can cause a late the diagnosis. The stage at diagnosis is the most important prognostic factor. Radiologic and endoscopic exams can be performed to achieve a specimen sample and to stage the disease. Early tumors can be treated properly with surgical resection. Adjuvant treatment for adenocarcinoma has not been studied in large trials, but it is indicated in extrapolating colon data. The treatment for advanced adenocarcinoma of the small intestine has only been studied in a few large cohorts. Treatment for other histologic types is discussed in a separated chapter.

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**Keywords** Small intestine · Cancer · Chemotherapy

## Abbreviations

GI	Gastrointestinal
UE	Upper Endoscopy
VCE	Video Capsule Endoscopy
CT	Computed Tomography
PET	Positron Emission Tomography
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
FOLFOX	Fluouracil plus Oxaliplatin
FOLFIRI	Fluouracil plus Irinotecan
PD-1	Programmed-Death Receptor 1
FDA	Food and Drug Administration
ESMO	European Society of Medical Oncology

## 19.1 Epidemiology and Clinical Presentation

Primary small intestine neoplasms are relatively rare, representing only 3% of all gastrointestinal (GI) cancers and 0.5% of all cancers in the United States [1]. Although there is a small incidence, a variety of histologic types can arise within the small intestine: carcinoid tumors, adenocarcinoma, sarcomas, and lymphomas. Recently, carcinoid tumors surpassed adenocarcinoma as the most frequent histologic type. Data from National Cancer Database between 1985 and 2005 showed that the proportion of carcinoid tumors increased from 28% to 44%, while the proportion of adenocarcinoma decreased from 42% to 33% [2]. Generally, carcinoid tumors are more frequent in the ileum, while adenocarcinoma affects the duodenum more often. Sarcomas and lymphomas can develop in the entire organ [2].

There are two histologic types of adenocarcinomas that must be differentiated: pancreatobiliary and intestinal. The first seems to have a worse prognosis [3]. Some hypotheses have been proposed to explain the lower incidence of small intestine adenocarcinoma compared to the large intestine [4]: (1) the increased liquid content and the more rapid transit may provide less exposure to carcinogens and less irritation and (2) the higher concentration of benzpyrene hydroxylase and the much lower bacterial load may result in less carcinogen metabolites.

Data from the United States revealed that the incidence of small intestine cancer is rising [5]. This epidemiologic change seems to be caused by an increase of >4-fold of carcinoid tumors [2]. The incidence is slightly higher in men (1.5:1) [6]. The mean age at diagnosis is 60–62 years and 67–68 years for sarcomas and lymphomas and for adenocarcinoma and carcinoid tumors, respectively [5].

As observed in colon cancer, most small intestine adenocarcinomas arise from adenomas; however, unlike the large intestine, there are few data on this issue [7]. Some hereditary cancer syndromes are related to the development of large and small intestine adenocarcinoma: hereditary non-polyposis colorectal cancer [8], familial adenomatous polyposis [9], and Peutz-Jeghers syndrome [10]. Patients with inflammatory bowel disease are at an increased risk for developing adenocarcinoma, according to the extent and duration of small bowel involvement [11]. There is an association between multiple endocrine neoplasia type I with rare cases of carcinoid tumor of the small intestine [12]. Risk factors for other histologic types are not yet completely known.

The main symptoms are abdominal pain, weight loss, nausea, and vomiting, GI bleeding, and intestinal obstruction. In the case of a duodenal primary mass, jaundice is a possible sign of the disease [13]. Since the symptoms are often vague and non-specific, the level of suspicion of small intestine neoplasms are often low, and this can result in the majority of patients being diagnosed with advanced disease (58%, stage III or IV) [14].

Carcinoid tumors of the small intestine are more frequently well differentiated. This means that these neoplasms usually have a characteristic morphologic aspect, and they can produce biologically active amines. The majority of these tumors are asymptomatic on presentation due to hepatic metabolism of the active amines and its indolent growth. Metastatic disease is present in 90% of symptomatic patients. The mass effect of the tumor is generally the cause of symptoms such as abdominal pain and obstruction. Carcinoid syndrome occurs when active amines have gained access to the blood circulation, and it is typically in the setting of liver metastasis [15]. Details on this syndrome are discussed in a separate chapter.

Primary GI lymphoma is the most common extranodal form of lymphoma. The stomach and small intestine are the most common sites [16]. More information on this subject can be found in another chapter. Epidemiology and clinical manifestation of GI stromal tumors are also discussed in another chapter.

## 19.2 Diagnosis and Staging

The vague and non-specific symptoms in combination with the lack of physical findings can delay the diagnosis for up to several months [17]. The stage of diagnosis is a prognostic factor for overall survival. Therefore, a higher suspicion is necessary when evaluating symptomatic patients. There are radiographic and endoscopic tests to help physicians determine the diagnosis and staging of small intestine cancer; however, there is not a consensus on the right sequence of tests.

Upper endoscopy (UE) may provide a direct evaluation of the mucosa, and it can provide a specimen sample and resection of benign lesions [18]. However, only the duodenum can be assessed by UE. Although colonoscopy can also provide a specimen sample and direct evaluation of the mucosa, it can only assess the terminal

ileum [19]. Wireless video capsule endoscopy (VCE) is an interesting option for evaluating the entire small intestine. In a meta-analysis of 24 studies, VCE failed to identify tumors in 20 of 106 cancers cases (false negative rate, 19%) [20]. In a retrospective study at Mount Sinai Medical Center from 2001–2003, 562 individuals with non-specific GI symptoms underwent VCE, which detected small intestine tumors in 8.9% of the patients with only one false-positive result [21]. However, VCE cannot be performed in patients with a high suspicion of GI obstruction, because there is a high risk of capsule retention, which necessitates emergency laparoscopy [22]. In addition, VCE cannot provide a specimen sample, and it is fundamental to determine the diagnosis of small intestine cancer. Alternatively, double balloon enteroscopy is a very good option when available. It can directly evaluate the small intestine and provide tissue sampling. However, it is a difficult technique, and it is not available at the majority of institutions. Enteroscopy is another possibility, it is a very long standing exam and available in a very few hospitals.

CT is very important in staging, especially of adenocarcinomas. It can provide an evaluation of local and distant commitment caused by the disease. CT can detect abnormalities in up to 80% of patients with small intestine neoplasms [23]. CT enterography is an option when there is suspicion of GI obstruction and enteroscopy cannot be performed. However, similar to VCE, CT enterography cannot provide a specimen sample. In a study on 219 patients with a high index of suspicion and normal endoscopy, CT enterography detected 155 abnormalities with 5 false-positives. Among 164 patients with a normal result, a small bowel tumor was later found in 9 [24]. PET is largely used in cases of lymphomas and stromal tumors; however, PET is not currently indicated for adenocarcinomas. It can be used to evaluate the response to initial treatment (i.e., a decrease in the uptake value) [25]. The Tumor, Node, and Metastasis Staging System of small intestine cancers is presented as follows [26].

### ***19.2.1 Adenocarcinoma Staging***

The 8th version of the American Joint Committee on Cancer (AJCC) released in 2017 changed the staging as follows:

For T3 and T4, there is not necessary to describe the extension of penetration into the retroperitoneum [27]. The reason is that it is not a validated prognostic factor. Moreover, it is not reliably reported in the pathology assessment [27].

Now, N1 is defined as one or two positive nodes and N2 as more than two positive nodes. The reason for this change is to harmonize small intestine cancer staging with the rest of the upper gastrointestinal tumors.

The last change is that although all histology are assigned TNM, it has a prognostic meaning only for adenocarcinoma.

The following is the most recent tumor staging classification for adenocarcinoma: Tx, the primary tumor cannot be assessed; T0, no evidence of a primary tumor; Tis, high-grade dysplasia or carcinoma in situ; T1a, the tumor is invading the

lamina propria; T1b, the tumor is invading the submucosa; T2, the tumor is invading the muscularis propria; T3, the tumor is invading through the muscularis propria into the subserosa or into the non-peritonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration; T4, the tumor is perforating the visceral peritoneum or is directly invading other organs or structures (including other loops of the small intestine and mesentery; the abdominal wall by way of the serosa; the duodenum only, with invasion of the pancreas or bile duct); Nx, the regional lymph nodes cannot be assessed; N0, no regional lymph node metastasis; N1, metastasis in one or two regional lymph nodes; N2, metastasis in  $\geq 3$  regional lymph nodes; M0, no distant metastasis; and M1, distant metastasis.

The following are the stages of adenocarcinoma: stage 0: Tis, N0, and M0; stage I: T1–2, N0, and M0; stage IIA: T3, N0, and M0; stage IIB: T4, N0, and M0; stage IIIA: any T, N1, or M0; stage IIIB, any T, N2, or M0; and stage IV: any T, N, or M1.

### 19.2.2 Carcinoid Tumors Staging

Regarding carcinoid tumors, AJCC 8th edition proposes a new classification of nodal involvement, called N2; stages I–IV were simplified without substages A or B [27]. Moreover, duodenum has now a specific classification apart from small intestine [27].

The following is the tumor staging classification for carcinoid tumors: Tx, a primary tumor cannot be assessed; T0, no evidence of a primary tumor; T1, the tumor is invading the lamina propria or submucosa and is  $\leq 1$  cm in size; T2, the tumor is invading the muscularis propria or is  $>1$  cm in size; T3, the tumor is invading through the muscularis propria into the subserosal tissue without penetrating the overlying serosa (jejunal or ileal tumors) or invading the pancreas or retroperitoneum (ampullary or duodenal tumors) or into the non-peritonealized tissues; T4, the tumor is invading the visceral peritoneum (serosa) or other organs. For any T, add (m) for multiple tumors. Nx indicates that the regional lymph nodes cannot be assessed; N0 represents no regional lymph nodes metastasis; N1 indicates regional lymph nodes metastasis less than 12 nodes; N2 is used for large mesenteric masses ( $>2$  cm) and/or extensive nodal deposits (12 or greater), especially those that encase the superior mesenteric vessels; M0, represents no distant metastasis; and M1, represents distant metastasis.

The following are the stages of carcinoid tumors: stage I: T1, N0, and M0; stage IIA: T2–3, N0, and M0; stage III: T4, N0, and M0 or any T, N1–2, and M0; and stage IV: any T, N, or M1.

### 19.2.3 Sarcomas Staging

The staging system of small intestine sarcoma is discussed in a separate chapter.

### **19.2.4 Lymphomas Staging**

Lymphomas of the small intestine have the same staging system as other lymphomas, and this subject is discussed in a separate chapter.

## **19.3 Treatment**

The treatment of carcinoid tumors, sarcomas, and lymphomas arising from the small intestine are discussed in separate chapters for each histologic subtype. The treatment of adenocarcinoma is discussed in the following.

### **19.3.1 Stages I and II**

Initial tumors can be treated with surgical resection, which can achieve a 5-year survival >75% [28, 29]. Duodenopancreatectomy is the best procedure for tumors arising from the first and second portions of the duodenum. However, for tumors arising in the third and fourth portions of the duodenum, local resection can be performed with much less morbidity and comparable rates of disease control [30].

### **19.3.2 Stage III (Metastasis to the Regional Lymph Nodes)**

There is a lack of information regarding the benefit of adjuvant therapy (chemotherapy, radiotherapy, or both) in the treatment of small intestine adenocarcinoma. A meta-analysis concluded that there were no suitable trials to analyze [31]. In a study on 146 patients undergoing curative resection, 56 relapsed at a median time of 25 months, and systemic was more frequent than local recurrence [32], except for adenocarcinoma of the duodenum [33]. Patients with metastasis to the lymph nodes have a 5-year survival rate shorter than patients with stage I or II disease (35%, 65%, and 48%, respectively) [14]. The number of lymph nodes resected (>10) is also an important prognostic factor for overall survival [34]. Few retrospective trials address this topic, and their results are conflicting.

In a retrospective analysis of 54 patients treated at the MD Anderson Cancer Center, adjuvant chemotherapy improved disease-free survival (hazard ratio = 0.27; 95% confidence interval: 0.07–0.98;  $P = 0.05$ ) with no benefit for overall survival ( $P = 0.23$ ) [35]. However, a large retrospective series on 491 patients by the Mayo Clinic did not show any benefit with adjuvant chemotherapy [36].

In a study on genome hybridization, a comparison between adenocarcinoma of the small intestine with colorectal and gastric adenocarcinoma showed that adenocarcinoma was more genetically similar to colorectal than stomach cancer

[37]. Because of the paucity of trials and this genetic pattern, it is acceptable to extrapolate the data from colorectal cancer and offer adjuvant chemotherapy to patients who underwent complete resection for positive lymph nodes. A common regimen is the combination of oxaliplatin and 5-fluorouracil (5-FU), because this was the regimen that showed improved survival over 5-FU and leucovorin alone in patients with colon cancer in the MOSAIC trial [38]. Based on the safety and activity of the combination of oxaliplatin and capecitabine in the metastatic setting, this regimen is also an option.

In addition, for duodenal adenocarcinomas with positive margins because of the high risk of local recurrence, adjuvant therapy with 5-FU based chemoradiotherapy in addition to a course of systemic therapy is a reasonable option [9].

### 19.3.3 Stage IV (*Metastatic Disease*)

Small intestine cancer is a rare disease, and it is very difficult to develop phase III trials in order to evaluate the best treatment approach. Several years ago, proximal neoplasms were treated like gastric cancers, and distal tumors were treated like colorectal neoplasms. In a retrospective series on 80 patients, the treatment regimen of cisplatin and 5-FU showed higher response rates and longer disease-free with no benefit for overall survival [39]. The most encouraging study was conducted by the MD Anderson Cancer Center, which included 31 patients. Among 25 metastatic individuals, the combination of capecitabine (750 mg/m<sup>2</sup> twice daily on days 1–14) and oxaliplatin (130 mg/m<sup>2</sup> on day 1, every 21 days) showed a 52% response rate (with 3 complete responses) and a median overall survival of 15.5 months [40]. The appropriate dose of capecitabine is still debatable, because several trials on colon cancer have used a dose of 850 mg/m<sup>2</sup> twice daily; however, the only evidence specific to the treatment of small intestine adenocarcinoma was described previously, and the study used 750 mg/m<sup>2</sup> twice daily. Another encouraging study was presented at the 2014 ASCO annual meeting, which used mFOLFOX 6 in a multicenter phase II trial with 24 patients; a 45% response rate was reported, and the median progression-free and overall survival were 5.9 months and 17.3 months, respectively [41]. In a retrospective French multicenter study, 93 patients were treated with different regimens of FOLFOX (48 patients), infusional 5-FU [10], FOLFIRI [19], and infusional 5-FU plus cisplatin [16]. Although this trial was not designed to compare treatment regimens, FOLFOX achieved a higher response rate (13 of 38 partial responses, 34%), a longer median disease-free survival (7.7 months), and a longer overall survival (17.8 months) [42].

As second-line treatment, a retrospective French study included 28 patients who were treated with FOLFIRI after failure with FOLFOX or infusional 5-FU. This trial demonstrated an objective response of 20%, a median disease-free survival of 3.2 months, and a median overall survival of 10.5 months [43].

The role of biologic or targeted therapy has not yet been established. Only a few case reports or small series exist on cases using bevacizumab or cetuximab.

Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy were used in a series of 17 patients, and a 1-year and 3-year survival rate of 52% and 23%, respectively, was reported. However, up to 47% of the individuals had complications from the treatment, and two required a surgical approach. Therefore, these treatments must be discussed on a case-by-case basis, and they can only be performed at centers with a high expertise [44].

### ***19.3.4 Future Perspectives – Immunotherapy***

Although there is not any specific study on immunotherapy for small intestine cancer, recent trials found that immune checkpoint inhibitors are effective against tumors with mismatch repair defect including small intestine cancer [45].

Tumors with mismatch repair defect have microsatellite instability, consequently, a large mutational burden. It is hypothesized that tumors with a higher mutational burden stimulate immune system more than tumors with lower mutational burden [46]. Pembrolizumab and nivolumab are monoclonal antibodies that stimulate lymphocytes against tumors by binding the lymphocyte Programmed Death Receptor 1 (PD-1). There are clinical trials assessing their efficacy for tumors with microsatellite instability, although only Pembrolizumab is approved by FDA in the US irrespective of the primary site. Pembrolizumab was studied in a study that included 86 patients with 12 different tumor types, including advanced small bowel cancers, whose tumors were mismatch repair deficient [47]. Approximately 9% of the tested small bowel adenocarcinomas were mismatch repair deficient. Among all included patients, the objective response rate was 53%, and complete response rate was 21%.

## **19.4 Follow-Up**

Small intestinal cancers are rare tumors; thus, there are no guidelines for post-treatment surveillance from the ASCO, National Comprehensive Cancer Network, or the European Society of Medical Oncology (ESMO). Patients can be followed according to published post-treatment surveillance guidelines for colon cancer. According to THE ESMO's guideline, patients may be re-evaluated using a history and physical examination plus CEA testing every 3–6 months for 3 years and then every 6–12 months for 2 years. CT scanning of the abdomen and the chest may be performed every 6–12 months for 3 years. Endoscopic surveillance may be performed at 1 year and then every 3–5 years [48].

### **Key Points**

Small intestinal neoplasms are relative rare.

Neuroendocrine tumors are more common than adenocarcinoma.



Adenocarcinoma treatment is almost all times extrapolated from colorectal cancer.

Immunotherapy showed promising results among patients with advanced mismatch repair deficient tumors.

### Multiple-Choice Questions

1. Choose from the options below, the most frequent tumor histology of small intestine cancer:

- (a) Adenocarcinoma
- (b) Carcinoid tumors
- (c) Sarcoma
- (d) Lymphoma
- (e) Squamous cell carcinoma

Answer: (b) Carcinoid tumors surpassed adenocarcinoma as the most frequent small intestine neoplasm.

2. What segment of small carcinoma is more common for adenocarcinoma?

- (a) Ileum
- (b) Duodenum
- (c) Vater ampola
- (d) Jejunum
- (e) None of the above

Answer: (b) Small intestine adenocarcinoma is more common in the duodenum.

3. Which statements of the following are correct regarding small intestine carcinogenesis:

- I. The increased liquid content and the more rapid transit may provide less exposure to carcinogens and less irritation
- II. Small intestine is related to genetic syndromes
- III. p53 inactivation is related with small intestine carcinogenesis
- IV. The higher concentration of benzpyrene hydroxylase and the much lower bacterial load may result in less carcinogen metabolites.

- (a) All of the above are correct
- (b) I, II and III
- (c) I, III and IV
- (d) I and IV
- (e) IV

Answer: (d) The two hypothesis for small intestine cancer are cited in I and IV.

4. A 62 years-old man started abdominal pain, weight loss and nausea 2 months ago. He visited a physician who suggested an upper endoscopy and colonoscopy.

Both exams were normal, the patient has no signal of GI obstruction, although she has a palpable periumbilical mass. What is the next step?

- (a) Stop investigation
- (b) Try a video capsule endoscopy
- (c) Try a PET-Scan
- (d) Perform an exploratory laparoscopy

Answer: (b) A video capsule endoscopy should demonstrate evidence of small intestine cancer in this patient.

5. A 57 years-old woman with a diagnostic of duodenum adenocarcinoma that invades the muscularis propria and spread to three locoregional lymphnodes. What is her tumor staging?

- (a) T1b N1 M0
- (b) T1b N2 M0
- (c) T2 N1 M0
- (d) T2 N2 M0
- (e) T2 N1 M1

Answer: (d) According to AJCC 8th Edition her staging is T2 N2 M0.

6. Which of the following is not a symptom of carcinoid syndrome?

- (a) Tachycardia
- (b) Diarrhea
- (c) Flushing
- (d) Extremities Tremor
- (e) Bleeding

Answer: (e) Bleeding is not a symptom of carcinoid syndrome. All other can be caused by systemic release of 5HT-3.

7. The 8th Edition of AJCC purposed a new Staging System for small intestine carcinoid tumors. Now, there is a new classification N2. What does it means?

- (a) Large mesenteric masses (>2 cm)
- (b) Extensive nodal deposits (12 or greater)
- (c) Lymph nodes that encase the superior mesenteric vessels
- (d) All of the above
- (e) None of the above

Answer: (d) All sentences are definitions of N2.

8. A 65 years-old patient with signal and symptoms suggestive of small intestine cancer presents to you with signal of partial GI obstruction. Which of the following exam is not indicated?

- (a) Upper Endoscopy
- (b) CT Endoscopy

- (c) PET-Scan
- (d) Video Capsule Endoscopy
- (e) None

Answer: (d) Video Capsule Endoscopy is contra indicated in cases with GI obstruction.

9. Somatostatin analogues are the cornerstone of carcinoid tumors treatment. What is the most common adverse event with this medication?
- (a) Nausea
  - (b) Diarrhea
  - (c) Gallbladder stone
  - (d) Anorexia
  - (e) Alopecia

Answer: (c) The most frequent adverse event seen with somatostatin analogues is gallbladder stone due to the low gallbladder mobility caused by somatostatin analogues.

10. Small intestine adenocarcinoma is a rare disease with a paucity of therapeutic options for advanced disease. Recently, immunotherapy suggested some activity among mismatch repair deficient tumors. Which mismatch repair proteins we test?
- (a) MSH 2
  - (b) MLH 1
  - (c) MSH 6
  - (d) PMS 2
  - (e) All of the above

Answer: (e) All of the above are proteins related to mismatch repair.

11. You ordered a immunohistochemistry assay to test mismatch repair proteins in the tumor of a patient with small intestine cancer. The results are MSH 2 negative, MLH 1 positive, PMS 2 positive and MSH 6 positive. What is the conclusion of the test?
- (a) Mismatch Repair deficient
  - (b) Microsatellite instability Low
  - (c) Mismatch Repair proficient
  - (d) Inconclusive
  - (e) None of the above

Answer: (a) A negative immunohistochemistry for any protein is a positive finding for mismatch repair deficiency or microsatellite instability.

### Clinical Case

A 62 years-old male started abdominal pain, anorexia, and weight loss 6 months ago. He made an Upper Endoscopy that found a tumor in the duodenum. After

tumor resection, he came in the clinic with the following pathology findings: well-differentiated intestinal adenocarcinoma of duodenum, pT2 pN1 cMx, tumor margin positive for tumor infiltration. The physical examination is normal and no image exams found any signal of metastatic disease.

Does this patient have indication for adjuvant therapy?

Although small intestine adenocarcinoma is a very rare disease, retrospective series found that adjuvant treatment prolonged survival compared to surgery alone.

What is the best strategy for adjuvant therapy in this case?

Once again, there is not any prospective trial to evaluate the best strategy for small intestine cancer adjuvant therapy. Even though, this patient was treated with 5-Fluoruracil based chemoradiation because of the neoplasm infiltration into tumor margins.

Is there any other recommendation in this case?

A majority of patients with resectable duodenum adenocarcinoma is treated with gastroduodenopancreatectomy. After this surgery, it is very important that this patient see a nutritionist in order to recovery his weight.

What is the follow-up in this case?

After chemoradiation, this patient is seen every 3 months with physical examination and CT during the two first years after treatment.

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# Chapter 20

## Liver Cancer



**Thayse Gardini Alvarenga, Pamela Carvalho Muniz, Hakaru Tadokoro, Ramon Andrade De Mello, and Nora Manoukian Forones**

**Abstract** Liver cancer is the fifth most common malignancy in the world and the second cause of death which translates its high virulence (Cancer W-IAoRo: GLOBALCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. IARC, Lyon, 2012). This cancer is the fifth most common malignancy in men (554.000 cases, 7, 5% of the total) and the ninth in women (228.000 cases, 3, 4%). The estimated 782.000 cases worldwide in 2012 that occur 83% in developed regions (50% in China alone).

**Keywords** Liver cancer · Targeted therapies · Sorafenib

### 20.1 Introduction

Liver cancer is the fifth most common malignancy in the world and the second cause of death which translates its high virulence [1].

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This cancer is the fifth most common malignancy in men (554.000 cases, 7, 5% of the total) and the ninth in women (228.000 cases, 3, 4%). The estimated 782.000 cases worldwide in 2012 that occur 83% in developed regions (50% in China alone) [1].

Its prevalence and incidence are directly related to its etiological factors, known as B and C virus infection and environmental factors, which is heterogeneous among the different age groups, between geographic regions, sex and ethnic groups [2].

Hepatocarcinoma (HCC) is associated with viral infections by B and C viruses in 78% of cases, which is strongly associated with a variation in their incidence around the world [3]. In China, for example, more than 90% of patients with HCC have hepatitis B [4].

There are several risk factors associated with the development of HCC: cirrhosis due to hepatitis B and C, chronic alcohol consumption, non-alcoholic steatohepatitis, obesity, and autoimmune hepatitis [5]. Recently, causes related to the insulin resistance syndrome have increased mainly in developed countries [2].

The therapeutic challenges of HCC therefore include not only the neoplastic disease itself but also the control of its etiological factors, so well established, and the management of hepatic function, commonly already impaired at the time of diagnosis of HCC. This chapter aims to discuss general aspects of liver cancer, its etiology, diagnostic methods and therapeutic possibilities according to the clinical stage.

## 20.2 Etiology

There are several etiological factors associated with HCC. Viral infections and diseases associated with chronic inflammation of the hepatic parenchyma will ultimately disrupt the cell cycle causing changes in the DNA of liver cells leading to the disordered proliferation of hepatocytes [6].

Some genetic alterations are frequently identified in HCC as cell cycle dysregulation associated with somatic mutations or loss of heterozygosity in TP53, silencing of CDKN2A or RB1, or CCND1 overexpression; increased angiogenesis accompanied by overexpression or amplification of VEGF, PDGF, and ANGPT2, decreased of apoptosis as a result of activation of survival signals such as nuclear factor kappa B and reactivation of TERT [7].

Chronic use of alcohol is among the most frequent etiological factor. Excess alcohol causes oxidative stress in the liver tissue that leads to cirrhosis.

Nonalcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) is also associated with HCC, and in the last decades there has been a significant increase in this disorder that is currently present in 30% of the population and about 90% in adults with morbid obesity [7]. In some countries the NASH is the main cause of HCC. In the United Kingdom 40% of the HCC are associated with NASH [8].

Other factors that trigger this neoplasm are chronic autoimmune hepatitis, cryptogenic cirrhosis, primary biliary cirrhosis, hereditary hemochromatosis, alpha 1 antitrypsin deficiency; metabolic alterations such as thyrosemia, galactosemia and porphyria cutanea tarda [5].

Environmental factors are also related to HCC such as use of androgen steroids, smoking and aflatoxin present in foods like rice [9].



## 20.3 Clinical Presentation

HCC is asymptomatic for much of its natural history. The clinical presentation most commonly is jaundice, malaise, anorexia and abdominal pain. Sometimes may occur spontaneous vascular rupture causing acute abdominal pain and distension, a potentially fatal event [10]. Paraneoplastic syndromes, although rare, also can occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia [11].

## 20.4 Diagnosis

Given the particular characteristics of HCC to imaging tests and their correlation with previously existing liver disease, biopsy in general may not be performed to close the diagnosis of the lesions. However, in some cases the biopsy is necessary: when a lesion is suspicious for malignancy but multiphasic CT or MRI results do not meet imaging criteria for HCC, in patients who are not considered high risk for developing HCC or in patients with conditions associated with formation of nonmalignant nodules that may be confused with HCC during imaging [12].

On imaging tests, HCC lesion is characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed venous phase [13].

A meta-analysis showed that CT and MRI are associated with higher sensitivity than ultrasonography without contrast for detection of HCC. The MRI is more sensitive than CT [14].

A serum AFP is not a sensitive or specific diagnostic test for HCC. AFP levels  $> 400$  ng/mL are observed only in a small percentage of patients with HCC.

The study analyzed a large series of HCC patients and concluded the low sensitivity (54%) of AFP in the diagnosis of this cancer [15].

## 20.5 Staging and Prognosis

The pathologic and clinical stage is done by evaluation of the tumor extension, lymph nodes and metastases. At 2017, the American Joint Cancer Committee (AJCC) Cancer Staging Manual published its eighth edition, as shown in Table 20.1 [10].

We classified each individual as to tumor size (T), number of lymph nodes affected (N) and presence of metastases (M), as below [10]:

- TX: primary tumor cannot be assessed
- T0: no evidence of primary tumor
- T1: solitary tumor  $\leq 2$  cm, or  $> 2$  cm without vascular invasion
  - T1a: solitary tumor  $\leq 2$  cm
  - T1b: solitary  $> 2$  cm without vascular invasion

**Table 20.1** TNM staging according to AJCC 8th Edition (AJCC)

Clinical Stage (CS)	T	N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Adapted from Amin [10]

- T2: solitary tumor > 2 cm with vascular invasion, or multiple tumors, none > 5 cm
- T3: Multiple tumors, at least one of which is > 5 cm
- T4: single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
- Nx: regional lymph nodes cannot be assessed
- N0: no regional lymph nodes metastases
- N1: regional lymph nodes metastases
- M0: no distant metastases
- M1: distant metastases

Systemic staging can be done with imaging examinations such as computed tomography, magnetic resonance imaging, and bone scintigraphy.

The thorax computadorized tomography (CT) is recommended since lung metastases are typically asymptomatic.

Bone scan is recommended if suspicious bone pain is present or cross-sectional imaging raises the possibility of bone metastases. Multiphasic contrast-enhanced CT or MRI of the abdomen and pelvis is also used in the evaluation of the HCC tumor burden to detect the presence of metastatic disease, nodal disease, and vascular invasion; to assess whether evidence of portal hypertension is present; to provide an estimate of the size and location of HCC and the extent of chronic liver disease [13].

Many attempts are being made to create a classification capable of encompassing factors arising from the underlying liver disease and the cancer itself, which contributes to subsequent therapeutic decisions.

Traditionally, existing classifications looked separately for tumor characteristics, such as tumor node metastasis (TNM), or for features of the underlying liver disease, such as Child-Pugh. Subsequent classifications have attempted to group the factors by trying to get a global view of the patient, such as Okuda's classification, although it still leaves out countless important factors relating to the tumor. Other

classifications with this intention of better grouping of the factors are the Barcelona clinic liver cancer staging (BCLC) and cancer of the liver Italian program (CLIP) [16] (Table 20.2, 20.3, 20.4 and 20.5).

According to the analysis performed on a cohort of 244 United States patients of any stage, the BCLC showed the best independent predictive power for survival

**Table 20.2** Child-pugh classification

Points	1	2	3
<b>Encephalopathy</b>	None	Minimal	Advanced
<b>Ascitis</b>	Absent	Controlled	Refractory
<b>Bilirrubin (mg/dL)</b>	<2	2-3	>3
<b>Albumin (g/dL)</b>	>3,5	2,8-3,5	<2,8
<b>Prothrombin (s)</b>	<4	4-6	>6

Adapted from Durand et al. [17]

**Table 20.3** Okuda classification

	Score 0	Score 1
<b>Tumor Size</b>	≤ 50% of the liver	>50% of the liver
<b>Albumin (g/dL)</b>	≥ 3	<3
<b>Bilirrubin (mg/dL)</b>	<3	≥3
<b>Ascitis</b>	Absent	Present

Adapted from Maida et al. [18]

**Table 20.4** BCLC classification

	0 (very early)	A (early)	B (intermediate)	C (advanced)	D (end stage)
<b>ECOG</b>	0	0	0	1-2	3-4
<b>Liver function</b>	Child-Pugh A/B	Child-Pugh A/B	Child-Pugh A/B	Child-Pugh A-B	Child-Pugh C
<b>Tumor stage</b>	Single	Single or 3 nodules <3cm	Multinodular	Vascular invasion/ extrahepatic spread	Any

Adapted from Maida et al. [18]

**Table 20.5** CLIP classification

	Score 0	Score1	Score 2
<b>Tumor morphology</b>	Uninodular and extension ≤ 50%	Multinodular and extension ≤ 50%	Massive or extension > 50%
<b>Child-Pugh score</b>	A	B	C
<b>AFP (ng/mL)</b>	<400	≥400	-
<b>Portal vein thrombosis</b>	Absent	Present	-

Adapted from Maida et al. [18]

when compared with the other 6 prognostic systems (TNM, CLIP, CUPI, JIS, GRETCH and Okuda) [19].

## 20.6 Treatment for Local Hepatocellular Cancer

### 20.6.1 Surgery Resection

It is important to remind that the management of patients with HCC is complicated by the presence of underlying liver disease.

Surgical resection of hepatic lesions is a more effective curative treatment option available without HCC management. There are, however, several limiting factors to make this feasible. There is, at first, an unquestionable need that there is enough liver remaining to preserve the function of the organ. Some techniques allow us to perform resection after an increase in liver volume with vascular embolization or ligations [20].

In patients whose etiology is not related to cirrhosis and had preserved liver function, major and repeated hepatic resections (in cases of relapses) have a better prognosis than in cirrhotic patients with viral etiology [21].

The curative intention of the treatment is a partial hepatectomy for patients with a solitary tumor of any size with no evidence of gross vascular invasion. Resection is possible while preserving greater than 30% functional liver. Portal vein embolization is now a well-accepted preoperative preparatory method for increasing the potential remnant liver volume and safety of resection [21].

A nationwide survey conducted by the Liver Cancer Study Group of Japan showed that approximately all of recurrences of hepatocellular carcinoma (HCC) were in the remnant liver, followed by lung, and then bone [22].

### **20.6.2 Liver Transplantation**

Liver transplantation is a potentially curative therapeutic for patients with early HCC, it remove tumor lesions, treats underlying liver cirrhosis, and avoids surgical complications associated with a small future lives remnant (FLR), but is limited by organ shortage and allocation, which causes patients to drop out from the waiting list [23].

For the better characterization of patients with good prognosis for liver transplantation, the Milan criteria include: single tumor  $\leq 5$  cm or three nodules  $\leq 3$  cm [24].

In an attempt to reach more patients without loss of benefit of the procedure, slightly more comprehensive criteria were established, known as the University of California San Francisco (UCSF) criteria: single lesion  $\leq 6.5$  cm in diameter or 2-lesions  $\leq 4.5$  cm with total tumor diameter  $\leq 8$  cm) [25].

A study from 2011 reinforces the applicability of the Milan criteria, especially when the orthotopic transplant will be done, and the use of UCSF criteria especially when will be performed a living donor transplantation [26].

A study published in 2008 in the Journal of Gastrointestinal Surgery compared hepatic resection versus transplantation in 379 patients with well-compensated cirrhosis and early stage HCC who underwent hepatic resection (245) or liver transplantation (134). Thirty-seven percent of patients had documented recurrence (resection: 50% versus transplantation: 14%), with a median follow-up time of 2.5 years. The 5 years overall survival was significantly better after liver transplantation (66%) compared with liver resection (46%) ( $P < 0.001$ ) [27].

The management of patients with early stage HCC and well-compensated hepatic cirrhosis remains controversial. Although surgical resection is recommended by many centers, hepatic transplantation has been increasingly indicated [27, 28].

### **20.6.3 Nonsurgery Therapies for Localized Disease**

Only some patients are able to perform surgical treatment, therefore alternative non-surgical treatments of the local disease have been developed as percutaneous ethanol injection (PEI), percutaneous acetic acid injection (PAI), microwave coagulation therapy (MCT), laser interstitial thermal ablation therapy, cryoablation therapy and radiofrequency ablation (RFA) [29].

The combined use of these therapy options may also be a therapeutic strategy, sometimes forming a bridge for transplantation or resection of the hepatic parenchyma [30].

According to a consensus recommendation from the American Hepato-Pancreato-Biliary Association, transarterial chemoembolization (TACE) is a standard treatment for unresectable HCC even if the portal vein is involved, and is useful for transplant lesion size as a predictor of response. (Schwarz, R. E) The combination of TACE and target therapy is already a reality and has proven to be effective [31].

Among other possible local treatment options, stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) were shown to be effective in inoperable disease [32].

## 20.7 Treatment for Advanced Hepatocellular Cancer

Systemic treatment in hepatocellular carcinoma has important limitations not only due to the evolution of neoplastic disease itself but also of established liver dysfunction.

The sensitivity to systemic chemotherapy as well as its tolerance are important limiting factors in the treatment of these patients. The better molecular knowledge of the disease and the hallmarks involved in HCC allowed the study of other effective drugs in this scenario, although in selected cases, chemotherapy plays its role.

In view of the importance of angiogenesis and signaling pathways through tyrosine kinase receptors, sorafenib, a multikinase inhibitor including vascular endothelial growth factor receptor (VEGFR2), confirms its role in the HCC treatment [33].

The phase III study SHARP trial evaluated 602 treatment-naïve patients randomizing them to use sorafenib or placebo in advanced disease and achieved overall survival gain with the use of sorafenib of 10.7 months compared to 7.9 months for patients who used placebo, which was statistically significant ( $p < 0.001$ ). Another outcome assessment performed in this study was the time for radiological progression, which was also significantly higher in patients who used the target therapy (5.5 months vs 2.8 months,  $p < 0.001$ ) [34].

As for the toxicity profile of sorafenib, the adverse effects most commonly seen in trials in the various geographic regions are hand-foot skin reaction, diarrhea, alopecia, fatigue, skin rash, anorexia and nausea [34, 35].

The use of sorafenib in the first line of HCC treatment was then established, but there is still doubt about the profile of patients who in fact benefit greatly from the use of this medication. The idea of a predictive biomarker is studied but still without data that allow us to refine its indication. A recent study suggests factors possibly related to worse overall survival, such as presence of macroscopic vascular invasion (MVI), high alpha-fetoprotein (AFP), and high neutrophil-to-lymphocyte ratio [36].

Given the heterogeneity of the studies included in the studies, both in relation to the degree of hepatic dysfunction (Child-Pugh) and etiologies (hepatitis B and C), some studies have attempted to stratify these groups in order to evaluate the safety of the use of sorafenib in these diverse populations, sometimes underrepresented in the studies carried out until then [37].

The benefit of sorafenib seems to be sustained even after transcatheter arterial chemoembolization [38].

The idea of associating systemic chemotherapy with sorafenib has been studied in a phase II study and appears to be acceptable with respect to safety, with gain in disease progression time (its primary endpoint) in favor of the combination [39]. The combination was performed with sorafenib at the dose of 800 mg daily and doxorubicin at 60 mg/m<sup>2</sup> every 21 days, and phase III study results are now awaited [40].

Another therapeutic option, especially for patients who do not tolerate sorafenib, was evaluated in a phase III study not yet published. Levatinib (an inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, as well as fibroblast growth factor receptors (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR) -alpha, KIT, and RET) if not lower in overall survival [41].

In a recent study, immunotherapy with Nivolumab appears as a useful therapeutic tool, and although still phase 1/2 study (CheckMate 040) the objective response rate and its duration are encouraging; based on such a study the FDA approved the medication for the second line of HCC treatment [42].

A study called KEYNOTE-240, underway, will evaluate the role of another immunotherapy in the second HCC treatment line, pembrolizumab [43].

Another antiangiogenic, but oral administration, was studied in the scenario of the second therapeutic line. Regorafenib, inhibitor of tyrosine kinases, including those associated with tumor angiogenesis, was evaluated in a phase 3 study, compared with placebo and improved overall survival with a hazard ratio of 0,63 ( $p < 0 \cdot 0001$ ) and the median survival was 10,6 months for regorafenib versus 7 · 8 months for placebo [44].

Although deterioration of liver function has to be taken into account as well as the profile of side effects and maintenance of patient's quality of life, offering systemic chemotherapy is still an option as long as the patient tolerates it.

Several chemotherapy regimens were tested, and a phase III study randomized patients to receive either doxorubicin or cisplatin, interferon, doxorubicin, and fluorouracil (PIAF) every 3 weeks, for up to six cycles. Although patients on PIAF had a higher overall response rate and better survival than patients on doxorubicin, the differences were not significant in addition to the combined regimen showed higher toxicity [45].

The use of doxorubicin monotherapy in this scenario is also possible [46].

Combinations of chemotherapeutic agents have also been evaluated for the treatment of advanced disease, among them we rule with and without platinum. Although widespread in the treatment of colorectal cancer, a study was conducted with the FOLFOX regimen, combining oxaliplatin with fluorouracil and leucovorin, which demonstrated a trend of benefit in OS for use of FOLFOX [47].

Other combinations have also been studied, namely gemcitabine and oxaliplatin and oxaliplatin and capecitabine.

## Questions

1. Which one is the **incorrect** alternative:

- (a) In the pivotal SHARP trial sorafenib has demonstrated a survival benefit over supportive care in advanced HCC.
- (b) Participants of the trial had good performance status and early compensated cirrhosis
- (c) SHARP Trial is a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial
- (d) **The use of sorafenib in the first line of HCC treatment wasn't established, because there is still doubt about the profile of patients who in fact benefit greatly from the use of this medication**

**Commentary:** SHARP trial evaluated 602 treatment-naive patients randomizing them to use sorafenib or placebo in advanced disease and achieved overall survival gain with the use of sorafenib of 10.7 months compared to 7.9 months for

patients who used placebo, which was statistically significant ( $p < 0.001$ ). Despite the extent of cirrhosis and performance status are critical features of HCC prognosis, the use of sorafenib in the first line of HCC treatment was established in view of its survival benefit.

2. Which one is the correct alternative:

- (a) **T1a: solitary tumor  $\leq 2$  cm**
- (b) T1b: solitary  $> 2$  cm with vascular invasion
- (c) T3: Multiple tumors, at least one of which is  $< 5$  cm
- (d) T2: solitary tumor  $< 2$  cm with vascular invasion

**Commentary:** According to AJCC 8<sup>a</sup> edition, T1a lesion are solitary tumors  $\leq 2$  cm.

3. The BCLC classification takes into account the following criteria:

- (a) **ECOG, liver function and tumor stage**
- (b) Tumor size, albumin, bilirubin, ascitis
- (c) Encephalopathy, ascitis, bilirubin, albumin, prothrombin
- (d) Tumor morphology, Child-Pugh score, AFP, Portal vein thrombosis

**Commentary:** According to BCLC criteria, the factors analyzed are: ECOG, liver function and tumor stage.

4. The CLIP classification takes into account the following criteria:

- (a) ECOG, liver function and tumor stage
- (b) Tumor size, albumin, bilirubin, ascitis
- (c) Encephalopathy, ascitis, bilirubin, albumin, prothrombin
- (d) **Tumor morphology, Child-Pugh score, AFP, Portal vein thrombosis**

**Commentary:** According to CLIP classification, the factors analyzed are: tumor morphology, Child-Pugh score, AFP and Portal vein thrombosis.

5. Some criteria are used to evaluate the possibility of performing liver transplantation in patients with HCC, including the Milan criteria and the University of California San Francisco (UCSF) criteria, which respectively define:

- (a) Single lesion  $\leq 6.5$  cm in diameter or 2- lesions  $\leq 4.5$  cm with total tumor diameter  $\leq 8$  cm and single tumor  $\leq 5$  cm or three nodules  $\leq 3$  cm.
- (b) **Single tumor  $\leq 5$  cm or three nodules  $\leq 3$  cm and single lesion  $\leq 6.5$  cm in diameter or 2- lesions  $\leq 4.5$  cm with total tumor diameter  $\leq 8$  cm.**
- (c) Single tumor  $\leq 3$  cm or three nodules  $\leq 5$  cm and single lesion  $> 6.5$  cm in diameter or 2 lesions  $> 4.5$  cm with total tumor diameter  $> 8$  cm.
- (d) Single lesion  $> 6.5$  cm in diameter or 2 lesions  $> 4.5$  cm with total tumor diameter  $> 8$  cm and single tumor  $\leq 3$  cm or three nodules  $\leq 5$  cm.



**Commentary:** The Milan criteria include: single tumor  $\leq 5$  cm or three nodules  $\leq 3$  cm and the UCSF criteria include single lesion  $\leq 6.5$  cm in diameter or 2- lesions  $\leq 4.5$  cm with total tumor diameter  $\leq 8$  cm.

6. The main etiological factor related to the development of hepatocarcinoma is:

- (a) Hemocromatosis
- (b) NASH
- (c) **Cirrhosis due to B and C viruses**
- (d) Autoimmune diseases

**Commentary:** Hepatocarcinoma is associated with viral infections by B and C viruses in 78% of cases.

7. Regarding the serum markers for diagnosis of neoplasias, the marker most related to hepatocarcinoma is:

- (a) CEA
- (b) **AFP**
- (c) CA19.9
- (d) CA125

**Commentary:** The marker most related to HCC's prediction is alpha fetoprotein (AFP).

8. Indicate the alternative that corresponds the etiological factor of Hepatocarcinoma:

- (a) Hepatitis B e C
- (b) Alpha 1 antitrypsin deficiency
- (c) Obesity
- (d) **All the options above**

**Commentary:** Hepatite B and C, Alpha 1 antitrypsin deficiency and obesity are the etiological factors of HCC.

9. Which of the following criteria is useful for the selection of patients suitable for liver transplantation?

- (a) single tumor  $\leq 5$  cm or three nodules  $\leq 3$  cm
- (b) patients with cirrhosis Child Pugh B or C
- (c) tumors without vascular invasion
- (d) **All the options above**

**Commentary:** Liver transplantation is a potentially curative therapeutic for patients with early HCC, it remove tumor lesions, treats underlying liver cirrhosis, and avoids surgical complications associated with a small future lives remnant. For the better characterization of patients with good prognosis for liver

transplantation, the Milan criteria include: single tumor  $\leq 5$  cm or three nodules  $\leq 3$  cm and without vascular invasion.

10. In relation to the HCC diagnosis indicate the correct alternative:

- (a) Biopsy is essential for the diagnosis
- (b) **The diagnosis can be made with imaging tests**
- (c) Biopsy is never needed for the diagnosis
- (d) A serum Alpha-fetoprotein AFP is a sensitive and specific diagnostic test for HCC

**Commentary:** Given the particular characteristics of HCC to imaging tests and their correlation with previously existing liver disease, biopsy in general may not be performed to close the diagnosis of the lesions. However, in some cases the biopsy is necessary.

11. Which of the following in biochemical abnormalities is a paraneoplastic syndrome associated with HCC:

- (a) **erythrocytosis**
- (b) hiperglycemia
- (c) hypocalcemia
- (d) hypopotassemia

**Commentary:** Paraneoplastic syndromes, although rare, also can occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia.

12. Which of the items corresponds to the characteristics of HCC in the CT:

- (a) presence of arterial hypervascularity
- (b) washout or hypointensity in the delayed venous phase
- (c) rapid increase contrast administration during arterial
- (d) **All the options above**

**Commentary:** On imaging tests, HCC lesion is characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed venous phase.

13. The most common site of metastasis of HCC is:

- (a) spleen
- (b) **lung**
- (c) stomach
- (d) bladder

**Commentary:** The most common site of metastasis is lung followed by bone.

14. Surgical resection of hepatic lesions is a curative treatment but it is necessary to preserve percentage of liver function. What is the minimum percentage required?
- (a) >50%
  - (b) 10%
  - (c) 20%
  - (d) **30%**

**Commentary:** Resection is possible while preserving greater than 30% functional liver.

15. Which one is the correct alternative:
- (a) **FDA approved Nivolumab for the second line of HCC treatment**
  - (b) The use Nivolumab in the first line of HCC treatment was established
  - (c) FOLFOX regimen, combining oxaliplatin with fluorouracil and leucovorin, which not demonstrated a benefit in overall survival
  - (d) Associating systemic chemotherapy with sorafenib is not an option in the treatment of HCC

**Commentary:** In a recent study, immunotherapy with Nivolumab appears as a useful therapeutic tool, and although still phase 1/2 study (CheckMate 040) the objective response rate and its duration are encouraging; based on such a study the FDA approved the medication for the second line of HCC treatment.

### Clinical Case

A 51 years male patient presented with weight loss of 5 kgs in 2 months. The patient was known to have hepatitis B virus for 6 years. In examination was detected hepatomegaly 4 cms, below the right costal margin. Laboratory evaluation showed elevation of liver enzymes (AST 78 U/L and ALT 89 U/L), albumin 3.5 g/L. Child-Pugh A. Computerized tomography (CT) scan of abdomen showed multiple lesions, the biggest of size 8,5 × 7,6 cms, all of them with area of central necrosis and early washout in arterial phase with no other alteration. Serum alfa-fetoprotein (AFP) level elevated (756 ng/ml). The diagnosis was HCC in a hepatitis B carrier. The proposal was to initiate sorafenib 800 mg/dia. In 2 months of use of the medication the patient evolved with multiple toxicities such as: hand-foot skin reaction, diarrhea, alopecia, fatigue, skin rash, anorexia and nausea which have become limiting to the continuity of treatment. The proposal was then to start Regorafenib as the second line.

### Questions and Comments

1. What is the diagnostic criteria for HCC in the imaging exam?
2. Are the side effects associated with the use of Sorafenib described in the case compatible with those commonly described in trials?
3. Comment on the second-line therapeutic option of the above case.

## Comments

1. On imaging tests, HCC lesion is characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed venous phase
2. As for the toxicity profile of sorafenib, the adverse effects most commonly seen in trials in the various geographic regions are hand-foot skin reaction, diarrhea, alopecia, fatigue, skin rash, anorexia and nausea.
3. RESORCE Trial studied regorafenib, an inhibitor of tyrosine kinases, in a phase 3 study in the scenario of the second therapeutic line, compared with placebo which improved overall survival with a hazard ratio of 0,63 ( $p < 0 \cdot 0001$ ) and the median survival was 10,6 months for regorafenib versus 7–8 months for placebo.

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# Chapter 21

## Pancreatic Cancer



**Georgios Antoniou, Ioannis Koutsounas, Panteleimon Kountourakis, Christos Pontas, and Ramon Andrade De Mello**

**Abstract** Pancreatic cancer most commonly refers to the carcinoma of the exocrine pancreas, a disease that presents a constant challenge in modern oncology, since it is characterized by significant morbidity and carries a uniformly ominous prognosis. Adenocarcinoma of the pancreas is largely perceived as inherently resistant to most of the currently available treatment options, hence needing a Multidisciplinary team (MDT) discussion to face the hydra that might defy easy solutions.

**Keywords** Pancreatic cancer · Nab-paclitaxel · Chemotherapy

### 21.1 Overview

Pancreatic cancer most commonly refers to the carcinoma of the exocrine pancreas, a disease that presents a constant challenge in modern oncology, since it is characterized by significant morbidity and carries a uniformly ominous prognosis.

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Adenocarcinoma of the pancreas is largely perceived as inherently resistant to most of the currently available treatment options, hence needing a Multidisciplinary team (MDT) discussion to face the hydra that might defy easy solutions. Potentially resectable disease might necessitate a more aggressive multimodality approach as early stage detection makes cure plausible. Patients in the advanced and metastatic setting, however, do not share the opportunity to bask in a treatment with curative intent and palliation is the primary aim. Cumulative rise in knowledge of cellular and molecular biology and emerging evidence for the efficacy of new agents promise more potent treatment options and eligible patients with advanced disease are urged to participate in clinical trials. In this chapter, we sought to summarize existing knowledge about pancreatic cancer and present novel and future therapeutic strategies.

## 21.2 Essential Practice Aphorisms

Pancreatic cancer is a versatile disease with interesting anatomical and geographic topography that carries a dismal global prognosis, even for potentially respectable disease. Early stages lack significant symptoms to alert both the patient as well as the clinician, which results in a delay in diagnosis with pernicious effect and those diagnosed as an emergency presentation have a lower rate of survival [1, 2]. Moreover, failure in reliable validated biomarkers and screening processes reflects a strategic impediment resulting in more advanced presentation, technically challenging operations with increased risks, frequently misapplied or abandoned. Just 15–20% of patients are candidates for a more aggressive treatment with curative intent at the time when diagnosis is reached. Even so, the 5-year survival following surgery for the localized node-negative disease fairly reaches 10% in major trials conducted.

Nearly 90% are adenocarcinomas arising from the exocrine ductal system (PDAC). The incidence rate for PDAC of the head has remained at 5.6 per 100,000, whereas the rate for body/tail has increased by 46% (to 1.6 per 100,000) between 1973 and 2002. The majority of pancreatic carcinomas occur within the head/neck of the pancreas with much less affecting the body and even less the tail. For all stages combined, the 1-year survival rate remains at the discouraging 19% and the 5-year survival does not exceed 4–6%, with patients with pancreatic head cancer carrying higher survival rates compared with those with body/tail cancers [3]

It is hence not surprising that although it is the twelfth most common cancer in the world with 338,000 new cases (178,161 men and 159,711 women) diagnosed in 2012 worldwide, yet it is the seventh most common cause of cancer-related deaths. The estimated 5-year prevalence of people in the world living with pancreatic cancer is 4.2 per 100,000, while incidence and mortality have the least of improvement among cancer types in all epidemiology surveys over the last 40 years. Interestingly,



it appears to have a distinct preference in the more industrialized parts of the world, affecting more the developed countries with 2.6 times higher rate compared with the less developed [4, 5].

### 21.3 Epidemiology and Statistics

Pancreatic cancer is an aggressive and abysmal disease with increasing frequency for both sexes over the last almost 30 years worldwide and a life expectancy counting in months. The disease carries one of the highest incident-to-mortality rates among cancer types with almost 39 people being diagnosed and 38 dying from the disease every hour around the world, respectively. 45,220 (22,740 men and 22,480 women) are the estimated new cases diagnosed in the USA in 2013 with 38,460 estimated deaths (19,480 men and 18,980 women), being the fourth leading cause for cancer-related deaths, representing the 6.6% of all cancer deaths in this country<sup>1</sup>. European age-standardised incidence rates (per 100,000) have remained constant (around 9.0) since 1993 in the UK, however, 8455 people have been diagnosed with pancreatic cancer in the year 2010, a number steadily rising from 7684 in 2007 [4]. The very low incidence and death rates, on the other hand, in countries like Tanzania and Bangladesh (0.35 and 0.45 per 100,000 respectively) mainly reflect the major geographic diversity that this disease represents.

Pooled epidemiology data suggest that the 5-year survival for localized pancreatic cancer can reach the startling, for this disease, 24.1%, however only a very small percentage (8.7%) is diagnosed at such an early stage. This ends up in a disappointing 9% for regional and 2% for metastatic disease.

Pancreatic cancer is more common with increasing age and slightly more common in men than women (men:women 1.12:1). Age has a powerful influence on the risk of pancreatic cancer. It is rather uncommon in younger individuals, albeit random cases can still occur (less than 10–15% of cases) and it is frequent in the elderly. Its frequency increases precipitously after the age of 50 years, with most patients being between 60 and 80 years old at the time of diagnosis with the 7th decade of age carrying the highest rates. While incidence is lower for those under the age of 50, the 1-year survival rate for this group of patients is markedly higher as well as the 5-year survival that drops considerably for those over 60 years. The median age at diagnosis is 71 years, 69 years in whites and 65 years in blacks. The incidence in Afro-Americans (17.6 men and 14.3 women per 100,000) is higher than whites in the USA (13.8 men and 10.7 women per 100,000), albeit more recent data suggest this racial difference show to abate [6]. Afro-Americans also have the highest death rates from the disease. The median age at death is 73 with the ages 75–84 carrying again the highest rates. Although some improvement is demonstrated over the last 40 years in survival curves, the scenery has not changed much with the 5-year relative survival rate still represented in single figure.

## 21.4 Risk Factors

### 21.4.1 Lifestyle Risk Factors

Interestingly, pancreatic cancer incidence has been associated with socio-economic deprivation although some studies do not share this notion [7, 8]. Bearing in mind the aforementioned geographic distribution of the disease, we then understand that relatively little is known yet regarding the risk factors contributing to pancreatic cancer. Epidemiologic studies have assisted, by providing data, in an attempt to establish environmental and lifestyle factors as well as genetic predisposition associated with an increased risk for the disease.

#### 21.4.1.1 Smoking

Smoking is the most common risk factor attributing to pancreatic cancer, a very much otherwise age-dependant disease. Data analysis from 12 case-control studies demonstrated statistically significant 2.2-fold (95% confidence interval [CI] 5 1.71–2.83) increased risk of pancreatic cancer for current smokers compared with never-smokers [9]. Cigarette smoking attributes almost 25% of all cases and showed to increase the risk by 27% for every five cigarettes smoked per day [10, 11]. Tobacco “fingerprint” was clearly demonstrated in the genotyping of tumors resected from nonsmokers harboring a maximum of 5 mutations, whereas the tumors from smokers had as many as 49 mutations, albeit they did not yield any characteristic profile [12]. Smoking has also the debilitating effect of earlier onset of pancreatic cancer, since it has been identified that heavy smokers were diagnosed around age 62, almost a decade earlier than the average age of 71 (HR of 2.69 (95% CI, 1.97–3.68, P = 0.019 for active smokers) [13]. Passive smoking, cigars and snuff are no less harmful wontedness. The European (EPIC) study showed that passive smoking can increase the risk of pancreatic cancer by 50% and more devastating, that tobacco smoke children exposure on a daily basis incur double the risk of contracting pancreatic cancer later in life [14, 15]. Pipe smoking and smokeless tobacco are also believed to increase the risk [16].

Smoking cessation however important in reducing the risk of developing and dying from cancer, takes a number of years to abolish the unhygienic effect. A significant mitigating trend in risk is seen over time since stopping cigarette smoking. After 20 years, risk estimates are similar to that of nonsmokers (OR 0.98 (0.77–1.23)  $p < 0.0001$ ) [9]. Furthermore, smoking may also account for the trend of female pancreatic cancer surge in the recent decades.

#### 21.4.1.2 Alcohol Consumption

Evidence for a positive association between heavy alcohol consumption and the risk of pancreatic cancer has been demonstrated in pooled analyses. Compared with abstainers and occasional drinkers (<1 drink per day) where no confirmed link has

been established, higher consumption levels lead to increased risk for pancreatic carcinogenesis (OR = 1.6, 95% confidence interval 1.2–2.2 for subjects drinking 9 drinks per day) [17]. Analysis by type of alcohol showed that the risk was increased for consumers of more than 4 drinks of wine per day (OR = 1.5; 95% CI 1.0–2.1; *p* value for trend 0.017), whereas no excess risk has been observed for consumption of beer.

#### 21.4.1.3 Coffee Consumption

Although former data from older studies have suggested a potential association of coffee ingestion in the tumorigenic process of pancreatic cancer, prospective data as well as a very recent meta-analysis have clearly demonstrated no appreciable connection between coffee drinking and this type of cancer [18, 19]. Despite caffeine and its byproducts have been accused of influencing cancer inception through DNA repair inhibition and mitotic event induction, roasted coffee is a complex mixture of a number of different chemicals and actually evidence may exist that it might also reduce pancreatic cancer risk, even with just 125 mL of coffee daily (RR, 0.96; 95% CI: 0.90–1.02) [20].

#### 21.4.1.4 Diet

Many studies have suggested the relationship of dietary habits and supplements with pancreatic cancer. Lower serum lycopene and selenium have been observed in individuals who later developed pancreatic cancer. However, a clear direct association has not been evinced between dietary or supplemental consumption of these nutrients [21]. The high intake of the so-called “Western” diet products, saturated fat and/or meat, smoked or processed meat in particular, seems to correlate with an increased risk, although it is hard to be absolute [22]. Observations and several studies have linked fresh fruits and vegetable intake with an inverse effect on risk for pancreatic cancer development and following a more balanced, high-quality diet, as scored by the HEI-2005 (consisting of higher fruit, vegetable and whole grains intake, milk, meat and beans, and oils found in fish, nuts and seeds combined with a much lower intake of saturated fat, sodium, solid fat, alcohol and added sugar) can have a protective effect by reducing the risk (HR 0.85, 95% CI 0.74–0.97). Interestingly, the benefit appears to be higher for overweighted/obese men (BMI  $\geq$  25 kg/m<sup>2</sup>) [23].

#### 21.4.1.5 Obesity

Evidence that greater body fatness forms a convincing cause for pancreatic cancer is largely supported by a number of studies. Individuals aged 14–39 years who were overweight (a BMI of 25–29.9) (highest odds ratio [OR], 1.67; 95% confidence interval [CI], 1.20–2.34) or obese (a BMI  $\geq$  30) from the ages of 20 to 49 years (highest OR, 2.58; 95% CI, 1.70–3.90) carry an associated increased risk of

pancreatic cancer, independent of diabetes status. The association observed was stronger in men (adjusted OR, 1.80; 95% CI, 1.45–2.23) than in women (adjusted OR, 1.32; 95% CI, 1.02–1.70) and in ever smokers (adjusted OR, 1.75; 95% CI, 1.37–2.22). Furthermore, subjects who were overweight or obese had an earlier onset of pancreatic cancer by 2–6 years (median age of onset was 64 years for patients with normal weight, 61 years for overweight patients [ $P = 0.02$ ], and 59 years for obese patients [ $P < 0.001$ ]). Obesity at an older age was further linked to a lower overall survival in patients with pancreatic cancer [24]. Higher BMI has also been associated with more advanced disease at diagnosis, with 72.5% of obese patients presenting with metastatic disease versus 59.4% of healthy-weight patients ( $\chi^2 p = 0.02$ ) [25]. Both general and abdominal fatness augment pancreatic cancer risk. Surprisingly however, among nonsmokers, risk increases even among persons within the normal BMI range and has an increment of 10% for a five-point increase in BMI (1.10 [95% confidence interval (CI) 1.07–1.14,  $I^2 = 19\%$ ]). Central obesity is also a significant risk factor (for a 0.1-unit increment in waist-to-hip ratio was 1.19 (95% CI 1.09–1.31,  $I^2 = 11\%$ ) [26]. Moderate physical activity demonstrated an inverse relation (RR 0.45, 95% CI 0.29–0.70) particularly for overweighted and obese subjects (BMI  $\geq 25$  kg/m<sup>2</sup>).

## 21.4.2 Medical Conditions

### 21.4.2.1 Diabetes

A positive association between long-standing type 2 diabetes mellitus (DM2) and pancreatic cancer has been identified (OR for DM2  $\geq 4$  years in a recent meta-analysis was 1.5 (95% CI 1.3–1.8) and newly diagnosed with DM individuals have an eightfold higher likelihood of pancreatic cancer diagnosis within 3 years of meeting criteria for DM compared to the general population, implying that unveiling new-onset diabetes could serve to denote an early diagnosis of pancreatic cancer [27, 28]. Long-standing diabetes is a risk factor for pancreatic cancer (RR 1.94 95% CI, 1.66–2.27 in the most recent meta-analysis) and new-onset diabetes can be an early manifestation of the disease [29, 30]. Pancreatic cancer induced hyperglycaemia may occur up to 24 months prior to the cancer diagnosis [27]. Several putative molecules with diabetogenic effect have been proposed in an attempt to establish a causal relation [31]. The prevalence of DM is markedly higher than in other well-known diabetogenic states such as morbid obesity, polycystic ovarian syndrome and pregnancy and existing strong epidemiologic evidence support the concept that pancreatic cancer-related DM can be distinguished from primary DM2, thus giving the opportunity to older patients with newly diagnosed DM to be screened for asymptomatic pancreatic cancer [27]. Patients with young-onset or type I diabetes have double the risk of pancreatic cancer (overall RR for pancreatic cancer 2.00, with 95% CI 1.37–3.01). A causality relation can not be established in this setting, given the rare frequency of pancreatic cancer in people under 25, however, seems more likely that type I diabetes precedes pancreatic cancer [32].

Oral antidiabetic drugs (including metformin and sulfonylurea) may play a role in the relationship between DM2 and pancreatic cancer, too. A meta-analysis in 2012 demonstrated that metformin decreased the pancreatic cancer risk by 62%, contrasted by a substantial independence from use of sulfonylurea [33]. However, data from the General Practice Research Database suggest that the decrease in pancreatic cancer risk associated with metformin is consistent only in women (adj. OR: 0.43, 95% CI: 0.23–0.80) and that both sulfonylureas ( $\geq 30$  prescriptions, adj. OR: 1.90, 95% CI: 1.32–2.74) and insulin use ( $\geq 40$  prescriptions, adj. OR: 2.29, 95% CI: 1.34–3.92) is associated with an increased risk of pancreatic cancer [34]. Based on current knowledge, metformin may exhibit its beneficial effect by direct molecular mechanisms of action involving activation of the AMP-activated protein kinase (AMPK), a protein kinase sensitive to deviations in the AMP/ATP ratio, inhibition of the mTOR pathway and by interfering in cell polarity and cell division, further to controlling hyperglycemia and hyperinsulinemia. Metformin blocks the proliferative effects of insulin and IGF-1 by blocking the PI3K/Akt/mTOR signaling pathway and by inhibiting cell division [35].

#### 21.4.2.2 Chronic Pancreatitis

Chronic inflammation of the pancreas is another risk factor for pancreatic cancer. A study from the International Pancreatitis Study Group reported 56 cases of pancreatic cancer in 2015 patients with chronic pancreatitis yielding a standardized incidence ratio (the ratio of observed to expected cases) of 26.3. The cumulative risk reached 1.8% at 10 years and 4% at 20 years, independent of the type of pancreatitis [36]. Interestingly, younger ( $< 65$  years) cases demonstrated stronger associations with previous ( $> 2$  years) pancreatitis (OR: 3.91, 95% CI: 2.53–6.04) than the older ( $\geq 65$  years) cases (OR: 1.68, 95% CI: 1.02–2.76; P value for interaction: 0.006). This association was stronger for intervals between diagnoses of pancreatitis and pancreatic cancer of greater than 2 years, when individuals with a history of chronic pancreatitis had a nearly threefold increased risk of pancreatic cancer (OR: 2.71, 95% CI: 1.96–3.74) and more potent at intervals of  $\leq 2$  years (OR: 13.56, 95% CI: 8.72–21.90), entailing a potential causative role of chronic inflammation in the development of pancreatic cancer or even a delay in the diagnosis of pancreatic cancer [37]. Yet, the population attributable fraction was estimated at 1.34% (95% CI: 0.612–2.07%), suggesting that a relatively small proportion of pancreatic cancer might be avoided if pancreatitis could be prevented [38].

#### 21.4.2.3 Inflammatory Bowel Disease

Patients before the age of 25 hospitalised for ulcerative colitis carry an ominous sevenfold risk increase for pancreatic cancer in comparison to the general population, albeit this hardly reaches a double-fold increased risk for those hospitalised for ulcerative colitis at a later age [39]. Those suffering with Crohn's disease are at a 75% increased risk of contracting pancreatic cancer and hospitalized patients above

the age of 64 have a 3.3-fold increased risk of pancreatic cancer (95% CI, 1.88–5.37) compared to younger patients (<25 years old) who run half the risk (1.54 95%CI, 0.00–8.82) [40].

#### 21.4.2.4 Gastric Ulcer and *H.pylori*

A diagnosis of gastric ulcer is linked to an increased risk of pancreatic cancer (RR, 1.83; 95% CI:1.13–2.97). The risk is highest for those whose cancer diagnosis is close in time to their gastric ulcer diagnosis (RR, 3.66; 95% CI:1.45–14 9.24), but can remain significantly increased even 10–19 years after gastric ulcer diagnosis (RR, 2.89; 95% CI:1.26–6.64) [41]. Particularly, subjects operated for their ulcer have a 2.1-fold increased risk for pancreatic cancer (95% CI 1.4–3.1) 20 years after gastric resection, while vagotomy does not. A 20% excess risk for pancreatic cancer (95% CI 10–40%) was also observed even in unoperated gastric ulcer patients, which increased to 50% (95% CI 10–110%) 15 years after first hospitalization (p for trend = 0.03) [42]. It has been suggested that formation of carcinogenic molecules, e.g. nitrosamines, secreted from bacteria colonising the stomach post-operatively may have a causative effect [43].

*Helicobacter pylori* (*H.pylori*) seropositivity has demonstrated a weak, however, statistically significant association with pancreatic cancer [44]. Recent data from a meta-analysis have linked *H.pylori* infection to an increased risk of pancreatic cancer (OR 1.47, 95% CI 1.2–1.8) [45]. A subgroup analysis failed to associate CagA positive *H.pylori* strains with an increased risk of pancreatic cancer. A connection between pancreatic cancer risk and CagA-negative *H.pylori* colonisation was found among individuals particularly with non-O blood type but not among those with O blood type (OR = 2.78, 95% CI = 1.49–5.20, P = 0.0014; OR = 1.28, 95% CI = 0.62–2.64, P = 0.51, respectively) [46]. Chronic hyperacidity has been proposed as a hypothetical mechanism to explain the relation of *H.pylori* infection and pancreatic cancer increased risk. However, there are studies that defy the aforementioned notion and data that prove no relation of duodenal ulcer to pancreatic cancer [41, 47].

#### 21.4.2.5 Hepatitis B & C

Exposure to Hepatitis B virus has been shown to predispose to pancreatic cancer. Individuals with anti-HBc-positive serology have 2.5-fold increased risk (95% CI, 1.5–4.2), those with past exposure to HBV with natural immunity a 2.3-fold (95% CI, 1.2–4.2), and a fourfold increased risk (95% CI, 1.4–11.1) exhibit those without natural immunity. Of interest, diabetes mellitus significantly modifies the risk of pancreatic cancer among patients with past exposure to HBV, who appear to have a 7.1-fold (95% CI, 1.7–28.7) increased risk for pancreatic cancer [48]. Past exposure to Hepatitis C virus seems also to result in an increased risk of pancreatic cancer (OR = 1.26; 95% CI, 1.03–1.50) [49]. Substantial variation between different

geographical areas in seroprevalence of HBV/HCV-antigens/antibodies and genotypes require further investigation to validate these findings.

#### 21.4.2.6 Periodontal Disease

Tooth loss and periodontal disease have been identified as risk factors for pancreatic cancer attributing a 50% increase in risk (HR = 1.54, 95% CI = 1.16–2.04) and a twofold increase (HR = 2.06, 95% CI: 1.14, 3.75) respectively [50, 51]. Systemic inflammation, pathogenic invasion into the blood stream and impaired or hyperactive immune response to periodontal infection might give an interpretation of the liaison.

#### 21.4.2.7 Aspirin and NSAID

Recent laboratory data adorn aspirin with a potential tumouricidal effect. However an epidemiologic report challenged this notion and investigated into whether both aspirin and NSAID increase the risk of pancreatic cancer. Processing data from the Nurses' Health study, raised the possibility of a dose-dependant tumourigenic effect of aspirin in women, who made significant use of more than 14 tablets on a weekly basis for at least 4 years (RR = 1.86, 95% CI = 1.03–3.35) [52]. Despite these data, a number of studies have either found no connection between aspirin use and pancreatic cancer risk or even revealed an inverse correlation revealing a benefit with the use of even 1 tablet on a daily basis (OR. 0.74, 95% CI: 0.60–0.91, P. 0.005), an effect that was valid even for low-dose aspirin consumers (OR 0.67, 95% CI: 0.49–0.92, P 0.013), even after adjusting for cancer stage, smoking status, or body mass index [53–55].

#### 21.4.2.8 Allergies

A surprising finding is that reported in people with a history of allergies, who carry a considerable reduced risk for pancreatic cancer (OR = 0.77; 95% CI, 0.63–0.95). More surprisingly, common allergens such as the mold demonstrate marked inverse associations (OR = 0.49; 95% CI, 0.32–0.75) and trends were shown for lower risks associated with increasing number of allergies ( $p = 0.0006$ ) and severity of allergic symptoms ( $p = 0.003$ ) [56]. Furthermore, allergies particularly related to atopy exhibit a reduced risk of pancreatic cancer (RR, 0.71; 95% CI, 0.64–0.80), especially those affecting the skin and reactions to insect bites, hay fever and respiratory allergies other than asthma. Hence, the hyperactive immune system of allergic individuals may operate in an increased surveillance mode and protect against pancreatic cancer development [57].

### 21.4.2.9 Previous Cancers

On the report of a large pooled analysis, people run a higher risk of developing pancreatic cancer within 10 years of a diagnosis of pharyngeal, laryngeal, gastric, biliary, pulmonary, cervical, corpus uteri, bladder and ocular cancer and 10 years or later following a diagnosis of cancers of the stomach, colon, gallbladder, breast, cervix, placenta, corpus uteri, ovary, testis, bladder, kidney and eye, as well as Hodgkin's and non-Hodgkin's lymphomas. These risk increases are probably partly due to the well-documented shared risk factor of tobacco use. The risk of pancreatic cancer was decreased however significantly after cancers of the rectum and the prostate. The elevated pancreatic cancer risk in young patients found among different types of cancer implies a genetic link. Radiotherapy treatment for the first cancer may also be an additional risk factor [58].

### 21.4.2.10 Psychological Stress

Epidemiologic studies have rarely been pre-occupied with the investigation of the potential detrimental role of psychological stress in the development of pancreatic cancer. Severe psychological stress induced by the drama of losing a child has been tested and was associated with a significant rise in pancreatic cancer risk (OR 1.09, 95%CI; 1.02–1.17). Women and people already suffering psychiatric illness had the greatest risk increase after child loss. The risk was greater during the first 5 years after the loss (OR 1.27, 95%CI; 1.12–1.45) providing some initial evidence that psychological stress could also account as a predisposing factor for pancreatic cancer [59]. Interestingly, it has also been implied that neurotransmitter responses to psychological stress may instigate pancreatic cancer progression through the activation of multiple cAMP-dependent pathways and concurrent suppression of endogenous GABA, which may act as a promising therapeutic target [60].

## 21.4.3 Hereditary Risk Factors

### 21.4.3.1 Familial Pancreatic Cancer

In addition to environmental and lifestyle factors, inherited genetic changes or a familial causative link can play an important role for pancreatic cancer. This is suggested by the fact that almost 5–10% of patients report to have a first-degree relative with the disease. Individuals with a family history of pancreatic cancer are at a moderately increased risk of developing pancreatic cancer themselves (multivariate-adjusted odds ratios (ORs) = 1.76, 95% (CI) = 1.19–2.61) [61]. People with at least one first degree relative diagnosed with pancreatic cancer have almost double the risk of people without pancreatic cancer in their family, which increases further if relatives were diagnosed before the age of 50 or if there are more than two cases in the family (standardized incidence ratio reached, SIR 17.02, CI 95% (7.34–33.5)



[62]. However, a responsible specific gene defect, although implied, has not yet been identified and hence there is no genetic test available to early detect the susceptibility of certain individuals with a positive family history. Relatives of familial pancreatic cancer patients have an increased risk of developing other cancer types, such as breast (1.66-fold, 95% CI 1.15–2.34), ovarian (2.05-fold, 95% CI 1.10–3.49), and bile duct cancers (2.89-fold, 95% CI 1.04–6.39) [63].

#### **21.4.3.2 Hereditary Pancreatitis**

Hereditary pancreatitis is a rare hereditary form of pancreatitis that accounts for a minority of pancreatic cancer cases, in which the patients suffer recurrent episodes of acute pancreatitis beginning in childhood, even before the age of five and which typically results in pancreatic insufficiency by early adulthood. It demonstrates two types of inheritance causing an autosomal dominant form, when mutations in the cationic trypsinogen gene (PRSS1) are identified, and an autosomal recessive form, when it is about mutations in the serine protease inhibitor gene (SPINK1) [64]. Hereditary pancreatitis remarkably increases by 58-fold (95% CI 23–105) the risk of developing pancreatic cancer and attributes a cumulative risk (by the age of 70) of 30–44%. Tobacco use and diabetes seem to further increase this risk. People with hereditary pancreatitis present a higher mortality rate compared to the general population and they often consider pancreatectomy as a prophylactic measure, however, total pancreatectomy associated risks and morbidity are serious co-variants in such a decision.

#### **21.4.3.3 Pancreatic Cancer Hereditary Susceptibility Syndromes**

A variety of different germline genetic syndromes have been identified and been linked to an increased risk of pancreatic cancer displaying a range of penetrance resulting in a lifetime risk for pancreatic cancer as well as for a number of malignancies. The contribution yet of these syndromes accounts for less than 1 out of 5 cases of pancreatic cancer, suggesting the potential existence of other yet unidentified susceptibility genes. They are particularly important because identification of a gene makes it possible to quantify the risk of pancreatic cancer, organize screening for highly susceptible individuals or early curable precancerous conditions. Besides, this is valuable for trial design and quantification of other associated malignancies. Noticeably, particular germline mutations may denote a susceptibility to certain chemotherapeutics or targeted therapies.

#### **21.4.3.4 BRCA and PALB2. Hereditary Breast and Ovarian Cancer**

Mutations in the BRCA gene family have been associated with malignancies, such as breast, ovarian, prostate, gastric and colon cancer. The prevalence of germline BRCA2 gene mutations in pancreatic cancer patients varies among different

populations and is particularly high in individuals of Ashkenazi Jewish decent, mounting up to even 10%. The BRCA2 gene mutations prevalence increases among pancreatic cancer patients alongside the increasing number of affected relatives. BRCA2 mutations can be found in as many as 12–16% of patients with familial pancreatic cancer [65]. However, a reasonable number of pancreatic cancer patients with germline BRCA2 mutations report no breast or ovarian cancers running in their family revealing that evaluation of penetrance of these genetic alterations needs yet to be determined. The role of germline mutations in BRCA1 is less clear and although studies have suggested that also carriers itself a 2.26-fold (95% CI 1.26–4.06) higher risk of pancreatic cancer, it is lower than the one observed with BRCA2 and needs to be further evident in literature as it may have significant clinical implications [66, 67].

PALB2 (partner and localizer of BRCA2) gene mutations have been identified in 1–3% of familial pancreatic cancer kindred's. PALB2 mutation carriers are also associated with an increased risk of breast cancer, although, not all patients with pancreatic cancer who are found to have germline PALB2 mutations report a personal or family history of breast cancer. The PALB2 protein binds with BRCA2 protein and stabilizes it in the nucleus; the generated BRCA2/PALB2 complex is part of the Fanconi Anaemia DNA repair pathway that acts in double-stranded DNA repair, which may prove such tumours sensitive to DNA cross-linking agents [68]. The link between BRCA and PALB2 gene mutations with pancreatic cancer underlines the necessity of obtaining a good family history.

#### 21.4.3.5 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by hamartomatous polyps in the alimentary system and pigmented macules of the lips, buccal mucosa and digits. Germline mutations in PRSS1 and STK11 genes, associated with the syndrome, attribute an up to 26% (95% CI 0.4–0.47) cumulative risk (at age 70) and a 76% (95% CI 36–160;  $p < 0.001$ ) relative risk of pancreatic cancer. Individuals with the Peutz-Jeghers Syndrome run a highly increased risk for pancreato-biliary cancer (RR 96%; 95% CI 53–174;  $p < 0.001$ ) and would be good candidates for early neoplasia screening once this kind of tests become available [69].

#### 21.4.3.6 Lynch Syndrome and Familial Adenomatous Polyposis (FAP)

Lynch syndrome is an autosomal dominant hereditary disease characterized by early onset colon cancer due to germline mutations in one of the DNA mismatch repair genes (hMSH2, hMLH1, hPMS1, hPMS2, or hMSH6/GTBP). Individuals with Lynch syndrome are found to have a predisposition for a variety of malignancies, such as endometrial, gastric, small intestinal, ureteral and pancreatic cancer. Families containing a mutation in a mismatch gene reported an 8.6-fold (95% CI 5

4.7–15.7) increased risk of pancreatic cancer, corresponding to a cumulative risk of 1.31% (95% confidence interval [CI], 0.31–2.32%) up to age 50 years and 3.68% (95% CI, 1.45–5.88%) up to age 70 years compared with the general population [70]. Lynch syndrome kindreds might also benefit from screening and surveillance, especially since cancers that occurring in these frequently have microsatellite instability (MSI1) and a distinct poorly differentiated medullary histopathology, that despite their poor differentiation carries a relative good prognosis. Patients with FAP may also be at increased risk for pancreatic adenocarcinoma (RR 4.46; 95% CL 1.2–11.4) as well as their risk relatives [71].

#### **21.4.3.7 Familial Atypical Multiple-Mole Melanoma (FAMMM) Syndrome**

Familial atypical multiple-mole melanoma (FAMMM) syndrome is a disorder associated with multiple nevi, cutaneous and ocular malignant melanomas, as well as pancreatic cancers and is characterized by germline mutations in the CDKN2A (also known as the multiple tumor suppressor-1) gene. Kindreds with a 19–base pair deletion in exon 2 of the p16/CDKN2A gene (the Leiden mutation) have a 38-fold increased risk of developing pancreatic cancer and lifetime (by age 75) 17% risk [72]. This suggests that family members with known p16/CDKN2A gene mutation would benefit from regular skin examination for nevi and melanomas, which should be part of the clinical examination for these patients and their relatives.

#### **21.4.3.8 Ataxia-Telangiectasia**

Next-generation sequencing has recently made it possible to identify deleterious mutations in the ataxia telangiectasia mutated (ATM) gene that may play an important role in familial pancreatic cancer predisposition. The ATM protein is a serine/threonine kinase involved in DNA double strand break repair. The disease is caused by the inheritance of bi-allelic deleterious mutations in the ATM gene and has a reported carrier frequency of 0.5–1% in the population. It is characterized by progressive cerebellar ataxia, oculomotor apraxia, telangiectasias of the conjunctiva and skin, immunodeficiency, sensitivity to ionizing radiation and an increased rate of malignancies, in particular lymphoma and leukemia, but now has become evident that also increases the risk of pancreatic cancer [73].

#### **21.4.3.9 Li-Fraumeni Syndrome**

Li-Fraumeni syndrome is a rare autosomal dominant cancer predisposition syndrome related to the development of a number of tumors of the soft tissue, ie sarcoma, osteosarcoma, as well as pre-menopausal breast cancer, brain tumors, adrenocortical carcinoma, and leukemias. These often occur in childhood or young

adulthood and survivors have an increased risk for multiple primary malignancies. It has also been associated with elevated risk for pancreatic cancer (RR 7.3, 95% CI; 2–19,  $p = 0.006$ ) [74]. Besides, CDKN2A is implicated in the TP53 pathway. Chompret criteria or Dutch recommendations do not incorporate pancreatic cancer for TP53 mutation testing.

#### **21.4.3.10 ABO Blood Group**

Blood group is determined by the presence or absence of glycoproteins (antigens) that are expressed on the surface of erythrocytes and several other cells, including pancreatic cancer cells and is a hereditary characteristic that has been linked with the risk of several gastrointestinal tumours, including pancreatic cancer. People with blood groups A, AB, or B were interestingly found to have a moderately increased risk of developing pancreatic cancer compared to those with group O (adjusted hazard ratios for incident pancreatic cancer 1.32 [95% CI; 1.02–1.72], 1.51 [95% CI; 1.02–2.23], and 1.72 [95% CI; 1.25–2.38], respectively) [75]. Albeit, a causative mechanism has not yet been elucidated, a genome-wide association study managed to identify variants in the ABO blood group gene (locus on 9q34 marked by the SNP rs505922) linked to a per-allele odds ratio of 1.20 for pancreatic cancer (95% CI; 1.12–1.28) [76].

### **21.5 Pathophysiology**

A number of clinically and pathologically distinct neoplasms arise in the pancreas. These neoplasms can be broadly divided pathologically into those that are typically solid and those that are usually cystic. This categorization parallels the primary radiologic appearances of these neoplasms, and it helps narrow the clinical differential diagnosis. Specific pathologic diagnoses within each of these 2 broad categories have important implications for patient management and prognosis. The treatment recommendations in the “Treatment” section of this review are specific for invasive ductal adenocarcinoma (“pancreatic cancer”) and may not apply completely to some of the other tumor types that can arise in the pancreas.

#### **21.5.1 Solid Tumors**

##### **21.5.1.1 Invasive Ductal Adenocarcinoma**

The commonest solid tumor is the invasive ductal adenocarcinoma (PDAC), more commonly called “pancreatic cancer. In this type of cancer the neoplastic cells form glands (adenomas) and infiltrates the pancreatic tissue. These cancers are usually

firm and solid and a number of their neoplastic cells can be extended far beyond the main tumor. Almost all adenocarcinomas infiltrating the nerves and extend along the perineural spaces. Another significant characteristic of these cancers is that they have the tendency to invade the small veins and locoregional lymph nodes. Those characteristics result in easy metastasis to the regional lymphatic spaces and the liver. This is the reason why most of the invasive ductal adenocarcinomas have already spread beyond the pancreas by the time of diagnosis and are not suitable for surgical resection.

The invasive ductal adenocarcinoma of the pancreas (PDAC) is the trigger for an intense desmoplastic reaction. This desmoplastic reaction is composed of inflammatory and endothelial cells, fibroblasts and provokes a significant increase of the interstitial fluid pressure within the tumor [77, 78]. This elevated pressure of the interstitial fluid considered as a barrier to perfusion of the tumor and that can explain the low attenuation seen on contrast-enhanced imaging. The elevated pressure can also act as a barrier to the permeation of therapeutic agents [79, 80]. The desmoplastic reaction should be taken seriously into account by the oncologists when planning the treatment of adenocarcinoma, because even the best therapeutic agents are not effective if they do not reach the tumor cells.

### **21.5.1.2 Other Solid Pancreatic Tumors**

#### **21.5.1.2.1 Adenosquamous Carcinoma**

Adenosquamous carcinoma is very aggressive type with poor prognosis. In spite of its aggressiveness and its poor prognosis, many patients with an adenosquamous carcinoma may still benefit from surgical resection of the tumor [81, 82]. Their main characteristic is that in addition to neoplastic cells, they tend to have a large component of squamous differentiation [81].

#### **21.5.1.3 Colloid Carcinoma**

Colloid carcinoma is also referred as gelatinous carcinoma. It is an infiltrating ductal epithelial tumor that produces mucin and is composed usually of cuboidal or columnar neoplastic cells. Their characteristic image is that of floating cells in mucin pools and this type of tumor have no ovarian type stroma [77]. They almost always arise in association with intraductal papillary mucinous neoplasms (IPMNs), and they have a much better prognosis than invasive ductal adenocarcinomas [83]. The better prognosis of the colloid carcinomas is related to their tendency to present clinically at a lower stage than invasive ductal adenocarcinomas [84].

#### 21.5.1.3.1 Medullary Carcinoma

Medullary carcinoma is composed of poorly differentiated cells, which are characterized by frequently extensive necrosis, pushing tumor borders, and lymphocytic inflammatory cell infiltrates. Under the microscope we can see pleomorphic nuclei with variable nucleoli. Some of the medullary carcinomas demonstrate microsatellite instability, and patients are more likely to have a history of cancer in their family or other syndromes associated with cancer, such as Lynch syndrome [85]. It carries a better prognosis than invasive ductal adenocarcinoma.

#### 21.5.1.3.2 Signet Ring Carcinoma

This type of pancreatic cancer is extremely rare and usually aggressive, occurring in less than 1% of pancreatic carcinomas. It entails individual neoplastic cells with a prominent mucin globule, giving a “signet ring” appearance to the cells [77]. Signet ring carcinomas except of pancreas can arise as well from breast or stomach, both of which can metastasize to the pancreas. For that reason the clinicians should be aware, because their metastasis can mimic a pancreatic primary.

#### 21.5.1.3.3 Undifferentiated Carcinomas

Undifferentiated carcinomas and undifferentiated carcinomas with osteoclast-like giant cells are very aggressive carcinomas associated with a very poor prognosis for patients [77].

#### 21.5.1.4 Pancreatic Neuroendocrine Tumors (PanNET)

NETs are the second most common type of solid neoplasms of the pancreas but they are less aggressive than invasive ductal adenocarcinomas. Their 10-year survival rate is 45% [77]. These neoplasms are clinically important since some may be associated with genetic predisposition syndromes such as von Hippel Lindau (VHL) and the Multiple Endocrine Neoplasia 1 (MEN1). Another reason of their clinical importance is that some PanNETs produce endocrine hormones. Those hormones circulating into the bloodstream provoke some clinical syndromes such as glucagonomas and insulinomas. Usually these are referred as functional PanNETs. The PanNETs are often well demarcated, soft, and solid neoplasms. The neoplastic cells of NETs are rich in vascularization and microscopically form trabeculae or nests. This rich vascularity explains the tendency of Pancreatic NETs to enhance with contrast.

The prognosis and management of functional NETs depends on the clinical syndrome produced, the topography of the tumor and if the NET has spread to lymph nodes near the pancreas or to other parts of the body such as the liver, lung, perito-

neum, or bone. The most important prognostic factors for NETs are tumor stage and grade. The stage of PanNET is determined by the size and the metastatic potential and the grade by the proliferation rate of the tumor cells [86].

### **21.5.1.5 Pancreatoblastoma**

Pancreatoblastoma is a rare form of pancreatic cancer. They are typically large, solid and soft tumors and usually occur in childhood ranging from 2 to 20 cm carrying a relatively good prognosis [77].

### **21.5.1.6 Acinar Carcinoma of the Pancreas**

It is a rare usually solid malignant exocrine tumor and is associated with increased serum lipase. Typically arise in the head of the pancreas and unfortunately is associated with poor prognosis [77].

## **21.5.2 Cystic Tumors**

The second broad category of pancreatic tumors is the cystic neoplasms. During the last years and with the extensive use of the Computer Tomography scan more and more patients have been diagnosed with cystic lesions in pancreas [87]. Many of those cysts are neoplastic and some of them will progress to invasive carcinomas if they will be left without treatment. For that reason, cystic neoplasms of the pancreas are giving us the opportunity to treat pancreatic neoplasia before an invasive cancer develops.

There are four main types of pancreatic cystic neoplasms:

1. Intraductal Papillary Mucinous Neoplasms (IPMNs)
2. Mucinous Cystic Neoplasms (MCNs)
3. Solid Pseudopapillary Neoplasms (SPNs).
4. Serous Cystic Neoplasms (SCNs)

### **21.5.2.1 Intraductal Papillary Mucinous Neoplasms**

This type of cystic neoplasm grows within the larger pancreatic ducts and the tumor cells produce a thick fluid. If they are left untreated they can progress from low grade dysplasia to high grade dysplasia and to invasive cancer. The patients should be followed up carefully, especially those who have had an IPMN resected in the past, because of their high risk for developing an invasive tumour [88].

### 21.5.2.2 Mucinous Cystic Neoplasms MCNs

This type of neoplasm arises in the tail of pancreas and occurs almost exclusively in women. Mucinous Cystic Neoplasms are composed of columnar mucin producing epithelium supported by ovarian type stroma and they do not arise in the pancreatic duct system. This ovarian type stroma connective tissue resembles the tissue normally found in the ovary. They are measuring between 6 and 10 cm. MCNs are composed from a large number of small cysts filled with thick mucin and this formation gives them their characteristic appearance. They can progress from low grade dysplasia to high grade and to invasive tumor such as the IPMNs. They should certainly be followed up carefully.

### 21.5.2.3 Solid Pseudopapillary Neoplasms

Solid Pseudopapillary Neoplasms are low grade malignant neoplasms typically round, measuring around 2–15 cm. The neoplastic cells of the lesion usually have uniform nuclei. Necrosis can occur in neoplasm and as cell death usually occurs distant from blood vessels a pseudopapillae can be formed. SPNs typically affects young women [89].

### 21.5.2.4 Serous Cystic Neoplasms

Serous Cystic Neoplasms are almost always entirely benign and they grow at slow pace. Should they grow large enough they can compress the nearby organs and then cause symptoms. SCNs may be associated with von Hippel-Lindau Syndrome and usually are found in the tail of the pancreas. They are formed from glycogen rich cuboidal cells which compose straw coloured fluid cysts. We can follow them up with safety and they should be resected only if they are large or if they cause symptoms [90].

## 21.5.3 Genes Associated with Pancreatic Neoplasias

Apart from BRCA there are four more cardinal genes associated with pancreatic cancer.

### 21.5.3.1 K-RAS Mutation

*K-RAS* is an oncogene on chromosome 12 that codes a protein called GTPase. This protein plays an important role in differentiation, proliferation and survival of cell through the mitogen-activated protein kinase (MAPK) pathway. *K-Ras* mutation



can be observed in up to 95% of invasive ductal adenocarcinomas [91, 92]. *K-Ras* point mutation can be detected early on in codons 12, 13 and 61, since it is one of the first genetic events that can occur in PDAC. Those codons can be easily identified and this is the reason why *K-Ras* could be one of the basic gene-tests for early diagnosis of pancreatic neoplasia, when early detection can deem the disease still curable [93].

### 21.5.3.2 The p16/CDKN2A Gene

The *p16/CDKN2A* gene is associated with family history of pancreatic cancer. *CDKN2A* is a tumor suppressor gene located on chromosome 9p and is not active in 95% of pancreatic neoplasms. This gene produces the protein p16 whose role is very important in cell cycle regulation, because p16 delays the progression of cells from G1 phase to S.

In pancreatic neoplasia the *CDKN2A* gene is losing his ability to produce p16 and as a result we can notice continuous unrestricted cell growth and proliferation of malignant cells [91].

### 21.5.3.3 Tumor Protein 53

*TP53* is another important tumor suppressor gene associated with pancreatic cancer. Is located in chromosome 17p and drives the production of protein 53 (p53). This protein can be found in the nucleus of the cells and regulates their division by direct binding with DNA. The significant role of p53 lies into that after cell exposure on radiation, ultraviolet rays or toxic materials defines if the damaged DNA should be repaired or the cell will self-destruct (apoptosis). *TP53* is not activated in 75% of pancreatic cancers and this decrease of activity can be observed early during the development of pancreatic tumor [91].

### 21.5.3.4 SMAD4 Tumor Suppressor Gene

The last major gene that can be identified in pancreatic cancer is the *SMAD4*. This gene was known previously as DPC4 and is located on chromosome 18q [94]. *SMAD4* mutation can be observed in approximately 55% of pancreatic neoplasms and plays a significant role in the function of TGF- $\beta$  proteins (transforming growth factor beta). TGF- $\beta$  proteins can regulate the differentiation, motility and proliferation of the cell. They can also promote angiogenesis and inhibit immune function of the cells. *SMAD4* gene mutation that is associated with poor prognosis in pancreatic neoplasms [95, 96].

## 21.6 Signs and Symptoms

Establishing a diagnosis of pancreatic cancer can be a complex process, posing a significant challenge to the clinician. Symptoms usually do not appear in the early stages, as the disease can remain silent until it spreads invading surrounding tissues or giving distant metastasis, or occasionally, signs and symptoms can be misinterpreted as presentation of other clinical conditions. Due to the diagnostic difficulties, pancreatic cancer recognition is usually achieved at advanced stages, which in combination with the aggressive clinical course of the disease, determine its poor prognosis. Delay in the diagnosis of pancreatic cancer by GPs or specialists, finally results in about 50% of pancreatic cancer patients presenting as emergency cases, while only 11% of patients are diagnosed through the 2-week referral system [97]. Symptoms and clinical features, if present, depend on the size and location of the tumour, as well as the presence of metastasis. More than one half of cases have distant metastases at the time of diagnosis. Additionally, initial signs and symptoms can be associated with resectability and prognosis of pancreatic cancer [98]. Lesions in the head of pancreas are often curable, as they can cause obstructive jaundice when they are still located inside the pancreatic gland, while patients with tumours in the body or tail generally present either with weight loss or vague pain, or even with symptoms associated to metastasis.

Painless and steadily increasing obstructive jaundice, due to biliary duct obstruction, is mainly associated with surgically resectable tumours in the head of pancreas, with more than two thirds of pancreatic cancers counting for this subcategory. The situation leads to increased levels of conjugated bilirubin and alkaline phosphatase in the blood. The urine is dark because of its high levels of conjugated bilirubin, while lack of stercobilinogen in the bowel results in pale-coloured faeces. Patients can experience *pruritus*, nausea, anorexia, and bruising caused by vitamin K malabsorption and reduced production of clotting factors. Body and tail tumors are much less likely to cause obstructive jaundice. Epigastric pain that radiates to the back may be present. Tumours in the body and tail usually do not cause symptoms until they present as locally advanced disease, extending to the peritoneum and spleen, or causing duodenal obstruction. Other symptoms include onset of diabetes, acute pancreatitis, steatorrhea and depression.

Physical examination findings may be normal. An enlarged, palpable gallbladder and the presence of painless jaundice (*Courvoisier's sign*) is up to 90% specific, but only 55% sensitive for malignant obstruction of the bile duct. Hepatomegaly is a common finding in advanced disease, while patients may present with ascites, palmar erythema, and spider angioma. Other findings associated with advanced or metastatic pancreatic cancer include left supraclavicular lymphadenopathy (*Virchow's node*) and recurring superficial thrombophlebitis (*Trousseau's sign*) [99].

## 21.7 Diagnosis

### 21.7.1 Imaging Modalities

#### 21.7.1.1 Ultrasound

Abdominal ultrasound (U/S) is an inexpensive, widely available imaging modality, mainly useful at the beginning of the diagnostic approach. Additionally, it is not invasive and lacks any kind of complications. U/S is the first examination in a patient with jaundice or abdominal pain, usually determining the aetiology of biliary dilatation, and either excluding or raising the suspicion for benign and malignant obstructions. The accuracy of conventional U/S for diagnosing pancreatic tumors is only 50–70%, percentage that is seriously affected by the operator's experience. Body and tail tumours are even more difficult to detect, due to the absence of biliary dilatation and the presence of bowel gas [100–102]. If the existence of a pancreatic mass cannot be excluded, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) should be used for further evaluation, as discussed below.

#### 21.7.1.2 Computed Tomography (CT): Conventional and Multidetector CT (MDCT)

Recent advances in technology have improved the accuracy of CT, with a reported sensitivity between 76% and 92% for diagnosing pancreatic cancer [103]. Due to the hypovascularity of pancreatic tumours, contrast agents should be always used, unless contraindicated. Multidetector CT (MDCT) provides higher image resolution than conventional CT. This technique allows better visualization of the pancreatic adenocarcinoma in relation to the superior mesenteric artery, celiac axis, superior mesenteric vein, and portal vein [104, 105]. Indirect signs, such as atrophic distal parenchyma, and abrupt cut off of the pancreatic duct dilatation (*interrupted duct sign*) are suggestive of pancreatic cancer. Extrahepatic biliary dilatation and pancreatic duct dilatation (*double duct sign*) may also be helpful [106]. The reported sensitivity, specificity and positive predictive value of the method, for predicting the resectability of pancreatic cancer, were 100, 72 and 89%, respectively [107]. MDCT with intravenous contrast is generally considered as the imaging procedure of choice for initial evaluation of patients suspected to have pancreatic cancer [108]. Main disadvantage of CT/MDCT remains the limited ability to detect isoattenuating tumours or small metastases to the liver or peritoneum [104, 106]. Even though pancreatic protocol CT is widely regarded to be superior to non-pancreatic protocol contrast MDCT for determining resectability, there is currently insufficient direct evidence to support this [109].

### 21.7.1.3 Magnetic Resonance Imaging (MRI)

MRI is a useful tool in imaging for pancreatic cancer, when a definite diagnosis cannot be established with ultrasound or MDCT. Due to their hypovascularity, pancreatic tumours are hypo intense on T1-weighted images in the venous phase, while they appear isointense on delayed images because of slow wash-in of contrast medium, usually gadolinium. MRI is superior to MDCT in detecting cystic lesions, isoattenuating or smaller tumours, and has better sensitivity in the presence of pancreatic fatty infiltration [110]. However, no statistically significant difference between the sensitivity of these two methods has been shown, overall (86% for CT vs. 84% for MRI), while their combination does not offer any additional diagnostic advantage. MRI is a radiation free, but expensive imaging method. Thus, the choice of MRI or CT usually depends upon local experience and availability [111].

### 21.7.1.4 Magnetic Resonance Cholangiopancreatography (MRCP)

A 3-D image of the pancreaticobiliary tree can be obtained with magnetic resonance cholangiopancreatography (MRCP), which is based on magnetic resonance technology. MRCP is very useful for detecting ductal narrowing, suggestive for the presence of a pancreatic tumour, or ruling out the existence of stones as a cause of biliary or pancreatic duct dilatation, while it can often contribute to the differential between chronic pancreatitis and pancreatic adenocarcinoma [112, 113]. It is as sensitive as Endoscopic Retrograde Cholangiopancreatography (ERCP) in the detection of pancreatic cancer, but lacks of complications, unlike ERCP [114].

### 21.7.1.5 Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is considered as a diagnostic, as well as therapeutic modality in patients with pancreatic cancer. Besides imaging, ERCP is helpful in the establishment of pancreatic cancer diagnosis using brush cytology and tissue biopsy samples. Although brush cytology has a limited sensitivity of 35–70% for the diagnosis of pancreatic cancer, the triple sampling combination of brush cytology, FNA and forceps biopsy of a stricture diagnosed during ERCP, improves the overall sensitivity to 77% [115]. The placement of a biliary stent with ERCP provides palliation of jaundice, and offers a less interventional alternative choice to surgery, especially in cases of unresectable cancers. In these circumstances, patients will benefit from chemotherapy with/without radiation. ERCP is also helpful preoperatively in resectable cancers. ERCP has a limited role in the staging of pancreatic cancer. Among the complications of this method, acute pancreatitis, gastrointestinal bleeding and perforation are the most common. ERCP plus EUS have been associated with a high diagnostic value for the detection of pancreatic neoplasms compared to ERCP or EUS alone [116].

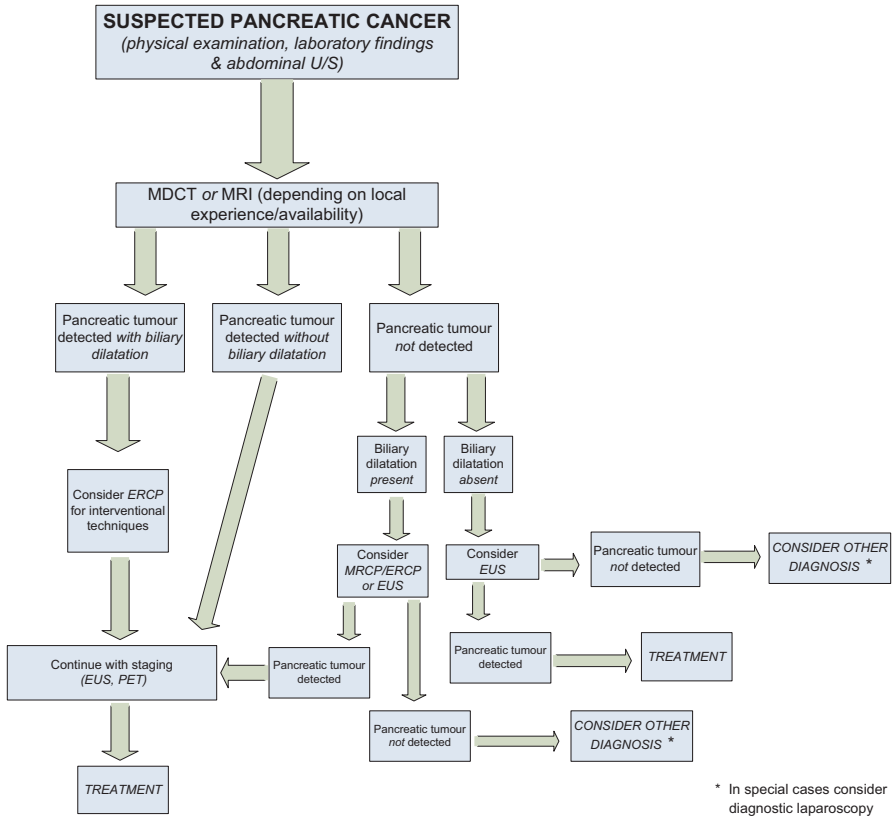
### 21.7.1.6 Positron Emission Tomography (PET)

Positron emission tomography (PET) scanning is a molecular imaging modality, using tissue accumulation of the radiotracer 18-fluorodeoxyglucose (FDG), a glucose analogue, as indicator of the metabolic activity of a lesion. Consequently, cancer can be distinguished from a benign lesion, or even inflammation, due to the higher accumulation of FDG. Sensitivity and specificity of this method range between 46%–71% and 63%–100%, respectively [117]. There are controversial studies regarding the superiority of PET scan compared to CT in identifying metastatic disease [118, 119]. However, PET scan is more sensitive for patients follow-up after chemoradiotherapy, as well as for estimation of disease recurrence [120–122]. PET/CT, offering a better image resolution than PET scan, has a higher reported sensitivity and specificity compared to conventional imaging for tumour staging and detection of metastases (89% and 100%, respectively), while the positive and negative predictive values of the method for pancreatic cancer were 91% and 64%, respectively [123].

### 21.7.1.7 Endoscopic Ultrasound (EUS)

Endoscopic Ultrasound (EUS) is the method used for establishing diagnosis when the other conventional methods have failed, or their findings are only suggestive for pancreatic cancer or non-specific. EUS also offers the ability to obtain specimens for histopathological diagnosis using EUS-guided fine needle aspiration (EUS-FNA). The specimens are subjected to cytologic examination and special immunostaining can be used for suspected neuroendocrine tumors [124]. The reported sensitivity of EUS-FNA for diagnosing pancreatic cancer ranges from 80% to 95% in various studies [125–127]. EUS-FNA was shown to be superior to ERCP for tissue sampling due to its higher success rates and less procedure-related complications [128]. The presence of obstructive jaundice and that of underlying chronic pancreatitis seem to reduce the accuracy of EUS-FNA for diagnosing pancreatic cancer. Especially in patients with both characteristics, the diagnostic accuracy of EUS-FNA is significantly lower [129]. EUS has a remarkable role in staging and is considered as an accurate pre-operative tool in the assessment of resectability in patients with pancreatic cancer. EUS also plays a role in identification and biopsy of locoregional metastatic lymph nodes [130, 131]. However, EUS has a limited accuracy for diagnosis of venous involvement by pancreatic cancer [132]. It was also shown that the presence of a biliary stent reduced the T-stage accuracy of EUS to 72% [133]. EUS elastography, which is considered as a recent and promising advance in GI endoscopy, is a non-invasive technique that measures tissue elasticity in real time [134]. EUS shares the same complications of other endoscopic procedures.

In conclusion, MDCT is the initial imaging method of choice in patients with clinical suspicion for pancreatic cancer. MRI stands as an alternative method when definite diagnosis is not achieved with MDCT. MRCP can be helpful in clarifying



**Fig. 21.1** Proposed diagnostic algorithm for pancreatic cancer

the nature of a biliary stricture, while ERCP also offers the ability to apply interventional techniques. EUS can set with the highest accuracy a definite diagnosis, apart from being a very useful tool for staging and determination of resectability. PET/CT, if available, can provide additional information regarding resectability, by ruling out metastatic disease. Finally, diagnostic laparoscopy may decrease the rate of unnecessary laparotomy in patients with pancreatic cancer found to have resectable disease on conventional imaging [135]. (Fig. 21.1).

### 21.7.2 Serological Diagnosis

The current broadly used serological marker for the diagnosis of pancreatic cancer in clinical practice is carbohydrate antigen 19.9 (CA19-9), which is a sialylated Lewis A-active pentasaccharide detected on the surface of mucins in pancreatic cancer patients serum. Although elevated CA19-9 levels have been associated with the

presence of pancreatic or biliary cancer, there are many benign situations in which this marker is increased [136]. CA19-9 is not a suitable marker to be used in screening of asymptomatic subjects for pancreatic cancer, due to its relatively poor sensitivity and specificity. CA19-9 is considered a helpful tool in differential diagnosis of pancreatic cancer from chronic pancreatitis with high sensitivity and specificity [137, 138]. As early recurrence can be expected in patients with high preoperative levels of CA19-9, measurement of CA19-9 has a significant prognostic value before the therapeutic decision of resection, while persistent elevated marker levels after resection are indicative of remnant disease [139–141]. CA 19-9 may serve as an *in vivo* marker for chemoradiotherapy sensitivity [142]. Additionally, CA19-9 values can be useful in distinguishing benign from malignant intraductal papillary mucinous tumors [143]. The diagnostic value of CA19-9 is limited in obstructive jaundice [144]. Overall, CA19-9 is not an adequate marker for the diagnosis of patients with pancreatic cancer, and according to the American Society of Clinical Oncology Tumor Markers Expert Panel, CA19.9 is recommended only for monitoring response to treatment [145, 146].

Although other promising markers have been reported for pancreatic cancer diagnosis, none of them has entered clinical use. This is mainly due to low sensitivity or specificity of these markers. The specific pathophysiology and microarchitecture of pancreatic cancer, which is poorly vascularized, might prevent certain molecules from passing into the circulation. Additionally, combining existent tumor markers with new ones, did not provide applicable panels [147]. Markers that have been investigated in diagnosis of pancreatic cancer include the carbohydrates CA 50, CA 125, CA 195, and CA 72-4. Other proteins, like MIC-1, PAM4, OPN, HSP27, TPS, TSGF, CAM17.1, PF4, and CEACAM1 have been studied with encouraging results, although not showing superiority to CA19-9. Consequently, despite testing many markers or their combinations, none of them has been implemented for clinical routine use besides CA 19-9. [148]. As curative resection is only possible in early stages of pancreatic cancer, an urgent need for novel serum markers for pancreatic cancer screening still remains.

## 21.8 Treatment Options

Pancreatic cancer is a complex disease with a wide diversity of patient population. Optimal multidisciplinary treatment approach much depends on a careful and accurate initial staging. Patients with limited disease extent (mainly Stage I/II disease) will be serious candidates to undergo surgical resection followed by adjuvant therapy or neoadjuvant therapy, albeit the latter still remains controversial. However, it might be the treatment of choice for the Stage III borderline resectable cancers prior to resection. Patients with Stage III locally advanced disease may be treated with chemotherapy and/or chemoradiotherapy, although, carefully selected patients can still be considered for surgical resection. Yet, the vast majority of these patients will develop metastatic disease. Patients with Stage IV disease and good performance

status (PS) may proceed to systemic therapy, while those with poor PS shall be given best supportive care (BSC).

### **21.8.1 Localised Disease-Surgical Perspective**

Although patients with localized PDAC disease will most benefit from a complete resection of the primary lesion, a number of different factors can affect the decision of surgery when selecting patients. The systemic nature of PDAC at diagnosis, the relatively low chance of long-term survival and the impact of pancreatectomy on quality of life are factors that need to be carefully assessed. Since the majority of these patients have locally invasive and/or micrometastatic disease at the time of operation, they run a high risk of both local and systemic recurrence following an operation with a potentially curative intent and a significant morbidity in 40–65% of patients and mortality up to 5% [149, 150]. Furthermore, despite improvements in surgical techniques over the last decades and perioperative patient care, pancreatic surgery is still associated with substantial perioperative morbidity and in-hospital mortality as well as significant impact on complete recovery to a normal quality of life, which can take up to 2–3 months even in the absence of any complication.

This is also important to consider for the formulation of a management plan and the implementation of neoadjuvant therapy through patient evaluation by a multidisciplinary team. Several factors, including stage, overall performance status, tumor biology, influence the final decision and significant comorbidities and age (> 70 years) can determine the ability of a patient to tolerate a major operation or a neoadjuvant approach [151]. Extensive metastatic disease at the time of diagnosis, locally infiltrative and rapidly progressing tumors indicate aggressive biology and in general, patients even with an early-stage but aggressive tumor biology are unlikely to benefit from local therapy such as surgical resection. Although, there is still no validated marker to characterize this aggressive biology, low serum CA19-9 levels and wild-type *SMAD4* gene status can identify patients with a more favorable tumor profile.

The appropriate operation required for a given patient is mainly determined by the location of the tumor. Pancreaticoduodenectomy (Whipple operation) is the surgery of choice for lesions arising in the head of the pancreas, while a distal pancreatectomy with an en bloc splenectomy may be required for tumors in the tail. However, masses of the neck and body may require a pancreaticoduodenectomy, distal pancreatectomy or, rarely, a total pancreatectomy. Other partial resections, like central pancreatectomy or enucleation techniques do not result in an sufficient lymphadenectomy and are not considered to have a potentially intent. Minimally invasive approaches offer, at least in theory, the merits of less scarring, less postoperative pain, less wound complications, and an earlier return to normal activity and despite the complexity of most pancreatectomies have recently been gaining ground, albeit their role in the management of patients with pancreatic cancer is not yet clear [152]. Pancreaticoduodenectomy morbidity rate has discouragingly remained



between in the range of 45%, even at high volume centers, where results show significantly better outcomes. The common postoperative morbid complications include delayed gastric emptying (15%), wound infection (8%), pancreatic fistula (5%), cardiac events (4%), abdominal abscess (4%), bile leakage (4%), haemorrhage (4%), sepsis (2%) and all other complications in less than 2% of patients. The median survival rate still lingers in less than 2 years (18 months) with a 5-year survival of around 20%. Negatively affecting factors include positive resection margin, histological grade and tumor size of 3 cm or greater (HR 1.6,  $p < 0.001$ ) and regional lymphadenopathy (HR 1.3,  $p = 0.05$ ) [153]. However, emerging non-operative biliary decompression and endoscopic therapies such as stents and non-invasive celiac plexus blocks have facilitated the drastic reduction of elective surgical palliation.

### 21.8.2 Neoadjuvant Therapy

Neoadjuvant therapy remains controversial in pancreatic cancer treatment, although theoretically it presents many advantages, especially in borderline resectable tumors. Among the advantages, it is considered that preoperative chemotherapy allows an early treatment of micrometastatic disease and may also induce tumour regression, reducing the risk of  $R_1$  resection or relapse after surgery. Other potential advantages include a reduced risk of peritoneal tumour implantation during surgery, and the chance of an in vivo assessment of tumour chemosensitivity. Finally, neoadjuvant treatment allows a better patient selection identifying those patients for whom surgery is unlikely to provide any benefit [12]. However, several studies have shown that resection after neoadjuvant chemoradiation (CRT) is associated with increased postoperative stay. It is finally important to note that in order to initiate neoadjuvant therapy, histological confirmation of pancreatic adenocarcinoma is required, unlike surgical resection [154].

Several studies have evaluated the role of neoadjuvant chemotherapy, radiotherapy, or combination of both in resectable pancreatic cancer. A phase II randomized trial studying patients with resectable PDAC receiving gemcitabine alone or a combination of gemcitabine with cisplatin, showed that the response rate and overall survival (OS) were better in combination arm [155]. Neoadjuvant CRT with gemcitabine concomitant to RT was studied on patients with localized pancreatic cancer. Median OS for the whole patients population was 22.7 months while patients who underwent surgery had a median OS of 34 months [156]. A phase II trial evaluated the combination of cisplatin and gemcitabine followed by gemcitabine-based CRT in patients with resectable PDAC. The median OS of all patients from the date of diagnosis was 17.4 months while patients who completed CRT and underwent surgery had a median OS of 31 months [157]. Also paclitaxel in combination with radiotherapy has been tested in patients with resectable PDAC, with moderate results [158]. Overall, patients who completed neoadjuvant CRT and underwent surgery had a higher chance of achieving  $R_0$  resection and a higher overall survival when compared to patients from historical data that underwent surgery without

receiving therapy. Nevertheless, CRT may not effectively decrease distant metastasis, as shown by the high rate of distant failure in these studies. Consequently, the role of neoadjuvant therapy in patients with resectable pancreatic cancer has not yet been clearly defined. Prospective controlled randomized trials are needed so as to estimate the benefit of neoadjuvant strategies compared to conventional adjuvant strategies. Presently, the use of neoadjuvant therapies should be considered in the context of a multidisciplinary approach, in order to identify patients at high risk for recurrence.

Borderline resectable pancreatic cancers (BRPC) have been recently defined as cancers with limited involvement of the mesenteric vessels. In this setting, resection may be technically possible, but carries a higher risk of  $R_1$  resection and early recurrence. Chemoradiotherapy is a common approach in such cases and seems to improve the percentage of patients undergoing radical resection. In a study, 7 out of 18 of BRPC patients who received gemcitabine-based chemoradiotherapy were finally resected. Chemoradiotherapy did not increase perioperative morbidity and mortality [159]. In another study, patients were treated with gemcitabine, docetaxel, and capecitabine followed by 5-FU based chemoradiotherapy with IMRT. Eleven patients (64.7%) out of 17 underwent resection and eight patients (47%) achieved an  $R_0$  resection. The median progression-free survival and OS were 10.48 months and 15.64 months, respectively [160]. Forty borderline resectable pancreatic cancer patients were treated with combined capecitabine-based chemoradiation. A total of 16 patients (46%) proceeded to surgery, with 88% having an  $R_0$  resection and median overall survival of 23 months [161]. A chemoradiotherapy regimen including gemcitabine and oxaliplatin on 68 BRPC and locally advanced pancreatic cancer (LAPC) patients was studied, and  $R_0$  resection was achieved in 36 of 43 patients that underwent surgery. The median overall survival was 18.2 months for all patients and 27.1 months for those who underwent resection [162]. The benefit of neoadjuvant therapies in BRPC was retrospectively reviewed between 1999 and 2006. Patients received neoadjuvant chemotherapy followed by radiation in combination with either 5-fluorouracil (5-FU), gemcitabine, capecitabine, or paclitaxel. Patients who completed the whole therapy including surgery had a significantly better clinical outcome (median OS of 40 months), compared to a median survival of 13 months in unresected patients. These results confirm a positive effect of neoadjuvant treatment in this setting, however, the high rates of disease relapse claim for more effective future treatments [163].

In LAPC patients, neoadjuvant gemcitabine-based combinations have proved to induce higher response rates compared to single agent gemcitabine [164]. A phase II trial, evaluated gemcitabine and oxaliplatin combination in LAPC patients, and after treatment, 39% of patients underwent curative resection, with a 69% of  $R_0$  resections. Median OS of patients who underwent tumor resection was 22 months compared with 12 months for those without resection [165]. In another study, patients received either cisplatin, epirubicin, 5-fluorouracil/capecitabine, and gemcitabine or the same regimen with docetaxel substituting epirubicin for 6 months, followed by radiotherapy. A high response rate was observed (47%) while stable disease was reported in 42% of patients [166]. A recent systematic review evaluat-

ing 111 trials that included 4394 pancreatic cancer patients, suggested that neoadjuvant treatment may be able to induce conversion to resectability in about one-third of LAPC patients [167]. In patients with borderline resectable or nonresectable pancreatic cancer, neoadjuvant therapy may achieve down-sizing of the tumour, increasing the probability of R<sub>0</sub> resections. Current data is not sufficient to define an optimal regimen in this setting. Combination chemotherapy appears to achieve higher response rates, while there is no strong evidence to support that chemoradiotherapy is superior to chemotherapy alone. More effective chemotherapeutic regimens, like FOLFIRINOX and nab-paclitaxel, are now tested, but the efficacy of these treatments remains to be determined in prospective clinical trials.

### **21.8.3 Adjuvant Treatment**

#### **21.8.3.1 Practice Establishing Studies**

Despite the intensity of the approaches with curative intent, PDAC demonstrates very high rates of both locoregional, most commonly the superior mesenteric artery margin, and distal recurrence necessitating postoperative therapy in the effort to reduce this risk. Patients typically need a period of 6–8 weeks to recover or might take even longer, much depending on the occurrence of adverse events. The optimal adjuvant treatment for PDAC patients remains elusive and there is still no worldwide consensus on which regimen is more effective than others, however, 6 months of a 5-FU-based or gemcitabine-based chemotherapy is an appropriate standard option. Application of 5-FU- or gemcitabine-based chemoradiation (CRT) (45 Gy directed to the tumor bed, surgical anastomoses and peripancreatic nodes with an additional 5–15 Gy boost to the tumor bed) during the postoperative period could be considered an option for R1 resections and patients whose risk of locoregional recurrence is higher. Moreover, the optimal time and sequence of AT is still debatable, yet, since the vast majority of patients will relapse with synchronous distant metastases, systemic treatment gains a priority followed by CRT, should the patient remain disease free after completion of chemotherapy [3].

In spite of the recent advances in the metastatic setting (discussed later in the metastatic disease), adjuvant treatment has lagged behind and despite that a variety of different agents and their combinations have been tested 5-FU or gemcitabine-based scheme remains the golden standard. Historical trials established the role of adjuvant therapy, however, have not managed to definitely address issues like optimal sequence, modality and regimen [168–170]. Next generation studies have evaluated the benefit of adjuvant systemic chemotherapy. The CONKO-001 multicenter randomized phase III trial from the group at Charite Onkologie Group in Germany randomized 368 patients to either adjuvant intravenous gemcitabine for a total of 6 cycles or observation, achieving nearly a doubling of median disease-free survival (DFS) (13.4 vs 6.9 mo, respectively;  $p < 0.001$ ), and improved median OS (22.8 vs 20.2 mo,  $p = 0.005$ ) thus establishing its pivotal role in the management of patients

in this setting [171]. Another study recently with a very similar design randomized 119 Japanese patients to receive either adjuvant gemcitabine or resection only with comparable results to the CONKO-001 trial [172]. However, despite the fact that median DFS was significantly improved (median DFS, 11.4 vs 5.0 months; HR = 0.60 (95% CI: 0.40–0.89);  $p = 0.01$ ), with an acceptable toxicity profile, the trial failed to show an OS improvement (median overall survival, 22.3 vs 18.4 months; HR = 0.77 (95% CI: 0.51–1.14);  $p = 0.19$ ). Differences in the sample size, the number of cycles of chemotherapy, weeks from operation to randomization and inclusion criteria regarding tumor markers applied.

The European Study Group for Pancreatic Cancer (ESPAC) investigators similarly conducted a study comparing GEM vs 5-FU (ESPAC-3v2) [173]. This was originally designed as a 3-arm study, in which patients were randomized to receive a 6-month course of 5FU/LCV (leucovorin), the same duration of GEM or observation alone. However, as data emerged from other adjuvant trials regarding the benefits of adjuvant chemotherapy for PDAC, the observation alone arm was dropped. Still, ESPAC-3 represents the largest trial of its kind with a total of 1088 patients randomized between the two treatment arms of bolus 5-FU daily with leucovorin for 5 days every 4 weeks or GEM weekly for 3 weeks every 4 weeks for 6 cycles in total. The OS was 23.0 months in the 5-FU group and 23.6 months in the gemcitabine group, with higher rates of stomatitis and diarrhea in the 5-FU group and higher rates of hematologic toxicity in the gemcitabine group, but without any difference in quality of life. Taken together, the CONKO and ESPAC trials established both 5-FU and GEM as effective options for adjuvant chemotherapy. Yet, the median OS for patients with resected pancreatic cancer dishearteningly remains approximately 20–22 months.

The role of adding radiation therapy in the adjuvant setting is still controversial and debatable between the coasts of the Atlantic. The Gastrointestinal Tumor Study Group (GITSG) trial in the 1980s was the first trial to show a survival benefit for adjuvant chemoradiation [168]. In this trial, patients with resected pancreatic cancer were randomized to either observation or to chemoradiation. Chemoradiation included a 40-Gy split course of radiation with a 2-week break after 20 Gy, given with concurrent bolus 5-FU (500 mg/m<sup>2</sup> on days 1–3 of each 20-Gy course of RT), followed by additional weekly 5-FU for 2 years or until progression. The median OS was 21 months in the treatment arm compared to 11 months in the observation arm (adjusted  $p = 0.03$ ) and actuarial 2-year survival rates (43% vs 18%). Criticism however arose for the relatively low RT dose, the small number of patients, and the fact that 25% of the patients on the treatment arm did not begin postoperative treatment for more than 10 weeks following resection, mostly secondary to poor or delayed postoperative recovery. Following closure of the study, an additional 30 patients were registered on the combined modality arm and a subsequent report that included these and the original 43 confirmed the initial survival benefit. The European Organization for Research and Treatment of Cancer (EORTC) trial randomized patients to observation or to chemoradiation with 40-Gy split course given identically to the GITSG trial, with continuous infusion 5-FU (25 mg/kg/day) during the first course of radiation therapy, and for 0, 3, or 5 days of the second course

(depending on toxicities) [169]. Although the OS was 12.6 months in the observation arm compared to 17.1 months in the treatment arm, this difference was not statistically significant neither was the 5-year survival (22% vs 28% for control and treated patients, respectively,  $p = 0.208$ ). However unlike the GITSG trial patients did not receive maintenance chemotherapy.

A third large multicenter trial (ESPAC-1;  $n = 289$ ) examined the role of both CHT and CRT in this setting [170]. The study used a 2-by-2 factorial design whereby patients were randomly assigned after surgery to 1 of 4 options: CHT alone, CRT alone, CRT followed by CHT or neither. It is worthwhile mentioning that ESPAC-1 used the GITSG RT regimen (AP/PA split course 20/10 + 20/10, although up to 60 Gy could be given, physician judging the final treatment dose), as did also the researchers in the EORTC trial. The four arms were ultimately combined in two comparison groups: CHT vs no CHT and CRT vs no CRT. With approximately 71 patients in each arm, patients who received CHT (5FU/LCV) had a significantly improved median OS over no treatment arm (20.1 vs 15.5 months, respectively;  $p = 0.009$ ). Surprisingly enough, patients on the CRT arm had a trend towards worse outcome (median OS: 15.9 vs 17.9 months, respectively;  $p = 0.05$ ). Interestingly, CRT did not reduce the risk of local relapse in this study. Investigators of the ESPAC-1 trial concluded that although CHT should be embraced as the standard of care following PDAC resection, CRT should not routinely be used, due to its deleterious effect. Of note, this study was heavily criticized because of a great deal of nonadherence within the trial, the suboptimal delivery and dosing of RT that potentially negated any survival benefit conferred by CRT with longer time-to-treatment in the CRT group and inclusion of R1 patients.

A separate study (RTOG 9704) conducted in the United States by the Radiation Therapy Oncology Group (RTOG) compared GEM with bolus 5-FU in the postoperative setting, in an effort to improve on chemoradiation therapy; patients on both arms received CRT (5040 cGy with concurrent continuous 5-FU infusion) between their first and second cycles of prescribed CHT [174]. Notably, for tumors located in the pancreatic head (388 out of 451 patients), those in the GEM group had a non statistically significant benefit in median OS that became more pronounced on multivariate analysis ( $p = 0.05$ ), with 3-year survival rates of 31% vs 22% in the 5FU group. Despite an initial trend to survival benefit for GEM, there has been no difference noticed in OS between GEM and 5FU at closure, whereas it has demonstrated a significantly more toxic profile (Grade 4 hematologic; 5-FU 1% vs GEM 14%). It has to be noted that despite criticism regarding difficulties in data interpretation due to surgical and pathology issues resulting from the lack of standardization, RTOG has established the importance of CA 19-9 in the management of PDAC patients, demonstrated improved local failure compared to earlier studies (25% for the gemcitabine arm and 30% for the 5-FU arm) and implied that higher radiation doses might be more effective in preventing local recurrence. The primary mode of failure, however, remained distant metastasis, occurring in >70% of patients, which highlights the need for better systemic therapies.

The limited systemic therapy options in the adjuvant setting have been expanded by a breakthrough phase III randomized trial with GEM versus S-1 for patients with

resectable disease (The Japanese Adjuvant Study Group of Pancreatic Cancer; JASPAC-01 study) after the safety and efficacy committee recommended early reporting of the results [175]. The study enrolled 385 Japanese patients with stage II and III disease over a period of 3 years and achieved its primary endpoint to prove S-1 non-inferior to GEM ( $p < 0.0001$  for non-inferiority,  $p < 0.0001$  for superiority). The 2-year survival rates were 70% vs 53% for S-1 and GEM, respectively, with lower relapse rates in the S-1 arm. The 2-year relapse free survival rates were 49% vs 29% for S-1 and GEM, respectively and S-1 proved to be well-tolerated, with over 70% of patients completing the therapy and significantly fewer deaths. The S-1 emerges as a potential alternative to standard GEM-based adjuvant CHT with the limitation of S-1's broad application in the West, secondary to metabolic differences between Asian and Caucasian ethnic groups, requiring use of potentially lower doses of the drug for Caucasian patients, as gastrointestinal side effects of S-1 are more severe among them. One possible explanation for this difference is that the pharmacokinetics are affected by polymorphisms in cytochrome CYP2A6 and consequently 5-FU concentrations in the plasma are more likely to be elevated in patients from Western countries. Hence, S-1 could be considered an alternative treatment option for populations of Asian origin, but still needs to be attested in appropriately designed trials, before it is immediately available for use to non-Asian populations.

Improvements in the delivery of radiation therapy now also offer more hope and newer technologies such as IMRT or SBRT that use multiple, modulated beams of radiation can limit the dose to surrounding normal structures and organs at risk and deliver higher doses of radiation to the tumor bed. The increased use of more 3-dimensional (3D) conformal planning has led to more focused radiation fields, and it has now become feasible to deliver higher doses of continuous chemoradiation without increasing toxicities. Data presented from 2 high-volume surgical centers combined, Johns Hopkins University and Mayo Clinic, reported on 1272 patients who had undergone surgical resection for pancreatic cancer and received postoperative CRT with a median dose of 50.4 Gy [176]. Both studies combined and independently demonstrated an improved survival and increased locoregional control with chemoradiation when compared to surgery alone (median survival 21.1 vs. 15.5 months,  $p < 0.001$ ; 2- and 5-year OS 44.7 vs. 34.6%; 22.3 vs. 16.1%,  $p < 0.001$ ). Chemoradiation merits were once again more evident in margin-positive and node-positive. Yet, this once more did not address the ongoing issue of optimal adjuvant modality, where the role of chemoradiation is less clear, leaving chemo-based systemic treatment as the upfront management plan [177].

### 21.8.3.2 Novel and Future Postoperative Approaches

Several smaller trials have also looked at other systemic therapies and used combinations of agents that have shown efficacy in the metastatic setting. The CAPRI trial integrated immunomodulation in the evaluation of adjuvant chemotherapy with 5FU versus CRT using cisplatin, interferon alpha-2b and 5FU, followed by 5FU

[178]. One hundred twenty two patients were randomized, the median survival for 5FU/LCV was 28.5 months (95% CI, 20.4–38.6 month), and the 2-year survival rate was 54% over a recruitment period of 3 years. The chemoradioimmunotherapy regimen has negatively affected the quality of life, because of its profound grade III/IV toxicity. Despite trial's failure to show any significant difference with respect to OS, the 3.6-month longer median survival underlines the potentially beneficial role of this experimental regimen for selected patients and raised questions on the importance and time of surgery as well as predictive marker innovation. Based on their biological properties numerous different agents, including taxanes, oral fluoropyrimidines, epothylons and targeting molecules, have been tested alone or in several combinations, yet, despite the initially promising results the majority failed to incorporate into practice and its use is rendered questionable.

Most recent data suggest that future perspectives have to focus on patient selection and more personalized approaches in an attempt to address the dispute over best treatment option. Low matrix metalloproteinase-7 (MMP-7) serum levels predicted an OS benefit from adjuvant GEM (HR = 1.39 (1.05–1.83),  $p = 0.0001$ ), but not 5-FU, implementing that patients with low MMP-7 serum levels might have a better chance benefiting from adjuvant GEM rather than 5FU [179]. MMP-7 is involved in the breakdown of extracellular matrix (ECM), tissue remodeling and plays a critical role in tumor progression via activation, degradation and shedding of non-ECM. An immunotherapy approach integrated to standard treatment seems promising, safe and demonstrates an OS that compares favorably with already published data in the literature for resected pancreatic cancer. Hyperacute immunotherapy approach (Algenpantucel-L) combined with chemotherapy (mean 12 doses, range 1–14) has been tested in the adjuvant setting demonstrating survival benefit (the 12-month disease-free survival was 62%, and the 12-month overall survival was 86%) [180]. The agent is well tolerated with a favorable toxicity profile and there is currently interest to evaluate its effectiveness for upfront use in multimodality approach in a phase III trial. A single-center phase II study, of 5-FU based chemoradiation combined with a pancreatic cancer vaccine of irradiated granulocyte-macrophage colony stimulating factor (GM-CSF) transfected allogenic whole-cell tumor lines conducted, has resulted in a median OS of 24.8 months (95% CI, 21.2–31.6) and patients who showed a CD8+ T-cell response to post-immunotherapy induction mesothelin demonstrated a higher likelihood of achieving prolonged disease free status. Additional boost immunotherapy given at regular intervals beyond 1 year postoperatively offer innovative concept in the treatment of respectable disease. Other vaccines such as K-Ras mutant vaccines and MUC1 peptide-loaded dendritic cell vaccines also have shown early promising results that need however to be reproduced in larger scale trials.

The integration of predictive and prognostic biomarkers in the management of PDAC is of paramount importance since it can facilitate the recognition and selection of those patients who will benefit the most and stratify patients into optimal disease management. Genomic analysis and research into the cellular uptake of GEM suggests that levels of human equilibrative nucleoside transport protein 1 (hENT1) alters resistance and predict sensitivity to the treatment, while expression

of other ribo- nucleotide reductase 1 (RRM2) and excision repair cross complementing gene 1 (ERCC1) are independent prognosticators associated with reduced relapse free survival (RFS) and OS after resection of pancreatic cancer [181]. Deleted in Pancreatic Cancer locus 4 (DPC4)/SMAD4 tumor suppressor gene status at initial diagnosis may contribute to patient selection. Loss of SMAD4 expression was highly correlated with widespread metastasis resulting in poor prognosis, whereas intact SMAD4 expression was highly correlated with a locally destructive phenotype [95]. C-X-C chemokine receptor type 4 (CXCR-4) is another independent negative prognostic factor and a predictor of distant relapse suggesting that anti-CXCR4 targeting therapies could be a promising approach in combination with cytotoxic chemotherapy in the adjuvant setting [182]. A growing body of evidence has established the role for systemic chemotherapy in the adjuvant setting and there is cumulative rise in knowledge of cellular and molecular biology. Vigorous efforts have been made to evaluate less toxic regimens and incorporate new agents into our arsenal against a disease with ominous prognosis even at earlier stages.

### **21.8.4 Systemic Treatment for the Metastatic Disease**

Despite the improved understanding of pancreatic cancer biology, the early detection rate remains low. Almost 70% of patients are diagnosed with advanced disease upon diagnosis and there is no doubt that systemic chemotherapy remains the standard of care in our armamentarium. The available data for first line treatment are robust (OS: 6–11 months), meanwhile the evidence for second line treatment is supported mainly by phase II and retrospective studies with poor survival expectancy (OS: 3–9 months) [183].

#### **21.8.4.1 Chemotherapy**

##### **21.8.4.1.1 Gemcitabine Monotherapy and Combination Regimens**

By the landmark study of Burris et al. in 1997, gemcitabine (GEM) became the standard of care. 63 patients received GEM vs. bolus 5-fluorouracil (5-FU) (n = 63). Survival (5.6 vs. 4.4 months,  $p = 0.0025$ ) and clinical benefit (regarding performance status and pain management, 23.8 vs. 4.8%,  $p = 0.0022$ ) were observed [184].

Combination therapies involving platinum analogs, 5-FU, and other agents have been investigated in phase II and III trials. However, most of these failed to reveal a significant survival benefit, and only improvement in PFS and ORR was revealed [185]. Therefore, the combination approach remains a matter of debate. Furthermore, the major criticism relates with studies' underpowered statistical design. In this context, meta-analyses performed comparing GEM alone vs. GEM+cytotoxic or GEM+platinum analog or GEM+5-FU showed risk reduction for the combination arms (HR: 0.91; 95% CI, 0.85–0.97/HR: 0.85; 95% CI:0.76–0.96,  $p = 0.010$ / HR: 0.90; 95% CI: 0.81–0.99,  $p = 0.03$ , respectively). No risk reduction was derived by



GEM-Irinotecan combination [186, 187]. GEM + Docetaxel +Capecitabine (GTX) combination showed encouraging results in retrospective studies with median (m) OS reaching 11.3 months [188]. Prospective studies are warranted to evaluate the efficacy of this promising regimen.

Reni and collaborators investigated the cisplatin, epirubicin, 5-FU, GEM regimen (PEFG) *vs.* monotherapy. Improved survival at 1 year (38.5 *vs.* 21.3%) and in addition PFS at 4 months (60 *vs.* 28%, HR: 0.46) for the combination arm were reported [189]. Moore et al. evaluated the combination of erlotinib to GEM. A statistically significant improvement of PFS (HR = 0.77,  $p = 0.004$ ) and OS (HR = 0.82,  $p = 0.038$ ) derived, but the improvement in m OS (6.24 *vs.* 5.91 months) was clinically meaningless and debatable. It should be also noted that patients with a rash grade > 2, usually developed during the first 2–4 weeks of treatment, had the greatest benefit compared with the patients without rash (10.5 *vs.* 5.3 months) [190]. In addition, GEM plus cetuximab or inhibitors of angiogenesis combinations (afibercept, axitinib, bevacizumab, sorafenib, sunitinib) failed to show any benefit [191–194]. Unfortunately, phase III studies failed to confirm phase II encouraging data focusing on angiogenesis pathway.

Von Hoff and coworkers investigated the nab-paclitaxel and GEM combination *vs.* GEM alone in MPACT trial. 861 patients were studied. For the combination arm clear superiority was demonstrated with regard to m OS (8.5 *vs.* 6.7 months, HR:0.72; 95%, 0.62–0.83;  $p < 0.001$ ), m PFS (5.5 *vs.* 3.7 months, HR:0.69; 95% CI, 0.58–0.82;  $p < 0.001$ ) and RR (23 *vs.* 7%,  $p < 0.001$ ). Grade 3 or higher most common events were neutropenia (38 *vs.* 27%), neuropathy (17 *vs.* 1%) and fatigue (17 *vs.* 7%) [195]. The rationale of nab-paclitaxel administration is based on SPARC (secreted protein acidic and rich in cysteine) protein binding which is overexpressed in the cancer microenvironment. Thus nab-paclitaxel by depleting tumor stroma renders a high concentration of chemotherapeutic agent in the tissue [196, 197].

#### 21.8.4.1.2 5-FU/Capecitabine Combination Regimens

The continuous 5-FU infusion and Oxaliplatin combination *vs.* single arms of both 5-FU and Oxaliplatin offered benefit with regard to mOS (9 *vs.* 2.4 *vs.* 3.4 months, respectively) [198]. Furthermore, similar results were derived by the comparison of CapOx *vs.* CapGEM *vs.* GEMOX for PFS (4.2, 5.7, 3.9) and OS (8.1, 9, 6.9 months, respectively) [199]. Further studies evaluated protracted *vs.* bolus 5-FU and combination with Cisplatin or Mitomycin C [200, 201]. No survival improvement was revealed.

#### 21.8.4.1.3 Irinotecan Doublet Combinations

In a phase II study, by a FOLFIRI regimen clear benefit was derived for OS, PFS and ORR [202]. On the contrary, GEM+ Irinotecan regimens did not offer any improvement [203].

#### 21.8.4.1.4 FOLFIRINOX Combination

In PRODIGE 4/ACCORD 11, a randomized phase III trial, conducted by Conroy and collaborators, a three drug combination FOLFIRINOX (infusional 5-FU/folinic acid, irinotecan, oxaliplatin) was evaluated vs. GEM alone. Improvement was derived for OS (11.1 vs. 6.8 months, HR: 0.57,  $p < 0.001$ ), PFS (6.4 vs. 3.3 months, HR: 0.47,  $p < 0.001$ ) and ORR (31.6 vs. 9.4%,  $p < 0.001$ ). Grade 3 or higher most common events for the combination arm were neutropenia (45.7 vs. 21%,  $p < 0.001$ ), febrile neutropenia (5.4 vs. 1.2%,  $p = 0.03$ ), sensory neuropathy (9 vs. 0,  $p < 0.001$ ) and diarrhea (12.7 vs. 1.8,  $p < 0.001$ ) [204].

#### 21.8.4.2 Immunotherapy

The unmet medical need to improve survival in pancreatic cancer patients directed research to investigate the field of immunotherapy. Unfortunately, promising data obtained by phase.

I and II studies of MUC1, CEA antigen pulsed dendritic cell vaccines or a telomerase peptide vaccine (GV1001) with GM-CSF did not translate into a statistically and clinically survival improvement when tested in phase III studies [205–208]. Preliminary results in a phase IB study that investigated GVAX [irradiated pancreatic cancer cells modified to elude granulocyte-macrophage colony-stimulating factor (GM-CSF) and produce an anti-tumor immune response] + Ipilimumab vs Ipilimumab alone appeared encouraging (5.5 vs. 3.3 months) [209]. GVAX and CRS207 (a listeria based vaccine) translated to a survival benefit (6.1 vs. 3.9 months, HR:0.59,  $p = 0.0172$ ) which was more clear among patients treated in 3rd line (5.7 vs. 3.9 months, HR:0.29,  $p = 0.0003$ ) [210].

#### 21.8.4.3 Future Directions

Targeting the stroma that interferes with the weak drug penetration and confers chemo-resistance appears an attractive target. Sonic Hedgehog pathway plays an important role in this context. In addition, TGF-B – instead of its critical role in pathogenesis, metastasis and angiogenesis- is an important partner in stromal regulation. Furthermore, the Notch pathway, Histone de-acetylation and DNA hypermethylation are thought to be important targets in pancreatic cancer. Results of PARP inhibitors in patients with BRCA1,2 mutations, and clarification of data on metformin's use are strongly awaited.

Although various therapy combinations have been found to improve survival expectancy significant toxicity is often associated. Young patients or in good performance status are candidates for GEM+ nab-paclitaxel or FOLFIRINOX combinations. To those with modest or poor performance status single agent GEM could be the option. Moreover, for patients with poor performance status best supportive care could be the alternative.

## 21.9 Palliation

### 21.9.1 *Quality of Life*

Pancreatic cancer carries a dismal prognosis at even the early stage and patients usually have a limited follow-up before they progress on to a more advanced stage. Therefore, much attention is focused upon palliation and symptom control and the decision to treat a patient with more aggressively must always take into account the impact upon a patient's quality of life (QoL). Toxicities from treatment may also contribute to the patient's symptom profile despite any clinical benefit response deriving from it. Several comprehensive report forms exist to evaluate patient's QoL, however, EORTC has developed a disease specific QoL module for pancreatic cancer (EORTC QLQ-PANC26), which has 26 questions and must be used in conjunction with the generic instrument EORTC Quality of Life Questionnaire-C30 (EORTC C-30). Yet, its utility is strongly restricted both in research and clinical practice, since patients particularly with severe and disabling disease as it is often difficult to complete. Supportive management of symptoms must be initiated early and aggressively to ensure patient comfort with early involvement of the palliative care facilities [211].

Pancreatic cancer frequently presents with pain even as initial symptom at the time of diagnosis. Initial assessment of pain should include evaluation of the intensity, frequency, duration, exacerbating and/or alleviating factors as well as a comprehensive history of current and previous pain medications along with documentation of any side effects encountered on these medications. This should be completed by clinical examination to influence decisions on implementation of the appropriate pharmacologic or procedural interventions. Patient symptoms may also complement as prognostic signs for treatment success and mortality and their response to symptom control may act as predictors of disease extent and response [212].

Albeit, palliative care or pain team should be actively involved in the management of symptoms like pain, the attending physician should be trained and feel comfortable starting the initial analgesic regimen. Opioids are generally thought the mainstay of pharmacologic management of pancreatic cancer pain. Initial therapy shall preferably consist of a short-acting opioid such as morphine or oxycodone. Collateral comorbidities of the patient like chronic kidney damage and/or hepatic impairment should also be taken into account when selecting the appropriate agent. A sustained-release opioid, along with a short-acting opioid for breakthrough pain, may be the next step of actions mainly in patients whose pain has been roughly under control, those with constant pain or those sleeping problems due to pain. Common side effects of opioids include sedation, constipation, pruritus, nausea, xerostomia and testosterone suppression in those on long-term therapy. Constipation is commonly addressed with stool softeners or bowel motility-promoting agents.

However, more advanced techniques might be needed for pain control. The most common and effective procedural intervention for is celiac plexus block [213].

Patients with pain refractory to increasing doses of opioids and those who suffer debilitating opioid-mediated side effects seem to benefit most from a celiac plexus block. Most patients relish a > 3 month period of pain relief on initial celiac plexus neurolysis yields, yet, subsequent celiac plexus neurolysis may be feasible in selected patients, its efficacy is seriously mitigated by disease progression. More invasive techniques such as intrathecal delivery of analgesia, via an implantable intrathecal drug delivery systems (IDDSs), might prove helpful especially for patients who have not achieved adequate pain relief. IDDSs managed to control pain, significantly relieve common drug toxicities, and improve survival in patients with refractory cancer pain [214].

Physical symptoms like fatigue, anorexia, cachexia, gastric outlet obstruction, insomnia, decreased appetite, dysgeusia, indigestion and certainly pain heavily impact on pancreatic cancer patients's psychology. Additionally fear of disease recurrence, severity or advanced stage is pervasive and can render the patient emotionally unstable. Depression is a common condition up to one fifth of patients and become debilitating since data suggest that patients who are depressed are more likely to have suboptimal treatment or poor response. Notably, depression may as well precede initial diagnosis raising that this might equally be a result of chemicals released by the tumor and not just a consequence of the psychological burden of the diagnosis [215]. Regardless of etiology, appropriate early detection and treatment is of paramount importance for the immense suffering it causes.

### **21.9.2 End of Life**

Pancreatic cancer is a disease with a grim natural history and albeit the aim for health care providers is prolonging life, assisting patients and their families when in distress through the arduous transitions precipitating all too often is equally as important. The multidisciplinary team decision to discontinue treatment is equally disappointing most of the times for both patients and their families as it is for doctors and it should involve patient, family, friends, and the healthcare team. However, it is important to clarify that ending cancer treatment does not necessarily mean ending care. A hospice placement is frequently recommended when prognosis is no longer than 6 months. It addresses all aspects of a patient and family's needs, including the physical (eg, pain relief), psychological, social, and spiritual or may be given at home. Nowadays, advanced services such as hospital to home care also exist and facilitate the serene transition to home reducing their suffering.

#### **Synopsis – Take Away Messages**

It is the twelfth most common cancer type but the seventh cause of death due to cancer with 10–20% familial or hereditary cases and increasing incidence. It carries one of the highest incident-to-mortality rates among cancer types with almost 39 people being diagnosed and 38 dying from the disease every hour around the world.

Lifestyle factors like tobacco use, alcohol, obesity and diet form significant risk factors. Several medical conditions and hereditary diseases predispose to pancreatic cancer as does the occurrence of other cancer types. Point mutations, especially of the KRAS family do occur and drive oncogenesis through the MAP-kinase pathway in addition to Tumor Suppressor Gene inactivation such as p16, p53, DPC4/SMAD inactivation and BRCA2 mutations. The research on further molecular events in pancreatic carcinogenesis (overexpression of EGFR, VEGF, MMPs, COX-2, hedgehog signaling, IGF-1 pathways) has not yet manage to produce any fruit in clinical practice. Resectable and early stage disease still carries the best chances of long-term survival and by that we mean mostly small tumors mainly in the head of the pancreas without any extrapancreatic spread, patent SMV and PV, definable tissue plan between the tumor and regional arterial structures (including the celiac axis and SMA). Neoplasms of the tail are considered of high risk for peritoneal seeding despite their potentially smaller size. Yet, locoregional and distant recurrence frequency reaches 80%.

Systemic treatment established by a german group (CONKO-001) and several meta-analyses demonstrated superiority of postoperative gemcitabine compared to surgery alone for patients with resected pancreatic cancer and is the mainstay of adjuvant therapy in Europe; however, combined CRT is preferred in the USA, based on historical trials and single center experiences. Based on ESPAC-3 both weekly gemcitabine and 5-FU/LV can be considered appropriate adjuvant treatment. CRT might have a role to play in node positive, borderline resectable or palliation in advanced unresectable disease. Targeted therapies have largely failed to produce any substantial outcome. The interest for treatment of the metastatic disease has been revived by the introduction of combinations like FOLFIRINOX and nab-paclitaxel for patients with good performance status, absence of biliary obstruction and no infectious complications after addressing the problem of significant expected toxicity. Other alternatives with combination capecitabine and GEM or GEM single agent have conferred some modest benefits. Treatment on relapse or progression is not equally well established, but 2nd line options include 5-FU-based regimens, such as FOLFOX, FOLFIRI or even single-agent capecitabine in patients who cannot tolerate combination treatments.

The majority of patients present with a wide variety of symptoms, which need to be addressed early on and patient and their family requires receiving support, both physical and psychological. Early Palliative Care and Pain team involvement is highly recommended, since prognosis is dismal and relapse highly likely. Health care professionals and attending clinicians need to be actively involved and a network of professional is required to promptly address patient's needs. Course of events and overall management plan should involve a variety of specialties within the MDT. MDT shall also take the decision for no further oncologic treatment and arrange for patient's appropriate placement for end of life therapies.

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# Chapter 22

## Ovarian Cancer



Renata Félix da Justa and Ramon Andrade De Mello

**Abstract** Ovarian cancer is the fifth most common type of cancer in women and the fourth most common cause of cancer death in them. The overall 5-year relative survival currently is between 30% and 40% across the globe. However, the disease typically presents at late stage when this rate is only 29%. Despite the public health significance, the etiology of this lethal disease is not completely understood but many associated risk factors have been identified. Ovarian tumors benign or malignant originate from one of three cell types: epithelial cells, stromal cells or germ cells. More than 90% of malignant ovarian tumors are of epithelial origin, 5–6% of tumors constitute sex cord-stromal tumors, and 2–3% are germ cell tumors. Staging of ovarian cancer is surgical and the International Federation of Gynecology and Obstetrics staging remains the most powerful indicator of prognosis. Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking, followed in most patients by systemic chemotherapy with or without Targeted Therapies. In the relapse setting, treatment considerations include the disease-free interval, existing toxicities from first-line treatment and volume of disease at the time of relapse.

**Keywords** Ovarian carcinoma · Review · Management · Epidemiology

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## 22.1 Introduction and Epidemiology

Ovarian cancer (OC) is the fifth most common type of cancer in women and the fourth most common cause of cancer death in them [59]. The estimated number of new OC cases is 239,000 worldwide annually, and 152,000 deaths from this cancer. The highest rates are seen in Eastern and Central Europe, 11.4 per 100,000 and 6.0 per 100,000, respectively [1].

The risk of a woman developing OC is 1 in 75, and her chance of dying of the disease is 1 in 100 [2]. The overall 5-year relative survival rate has seen only very modest increases (2–4%) since 1995 [3]. Currently this rate is between 30–40% across the globe. However, the disease typically presents at late stage when the 5-year relative survival rate is only 29%. Few cases (15%) are diagnosed with localized tumor (stage 1) when the 5-year survival rate is 92% [2].

Despite the public health significance, the etiology of this lethal disease is not completely understood but many associated risk factors have been identified. This disease is predominantly in older, postmenopausal women (> 80% over 50 years). In relation to reproductive history, women who have had multiple pregnancies have a lower risk than those with fewer pregnancies, who in turn have a lower risk than nulliparous women. Early menarche and late menopause also seem to contribute to a greater risk. Use of the oral contraceptive pill, tubal ligation, breastfeeding and suppression of ovulation offer protection against OC.

In relation to family history women with a first-degree relative have more than a twofold increase in risk of ovarian cancer compared with women with no family history. However, only 10% of ovarian cancer cases have an identifiable genetic mutation. An inherited BRCA 1 mutated gene confers a 15–45% lifetime risk of developing OC and BRCA 2 mutated gene increases to 10–20%. Women with hereditary OC tend to develop the disease approximately 10 years earlier than women with non-hereditary OC [14, 59].

## 22.2 Pathology

Ovarian tumors benign or malignant originate from one of three cell types: epithelial cells, stromal cells or germ cells. More than 90% of malignant ovarian tumors are of epithelial origin, 5–6% of tumors constitute sex cord-stromal tumors, and 2–3% are germ cell tumors [4, 7]. (Table 22.1).

High-grade serous carcinoma is the most common histological type (70–80%), followed by endometrioid (10%), clear cell (5–10%), mucinous (3%), and low-grade serous (<5%) [8, 9]. Subtype and grade have prognostic importance [5]. Grade is a number of grading systems [1–3] which are defined according to tumour characteristics: architectural features, mitotic counts and nuclear atypia [6].

Low-grade serous tumours tend to present at a younger age and to do not respond to traditional chemotherapy regimens, but have a longer survival compared with

**Table 22.1** Histological subtypes of ovarian tumors

Epithelial Ovarian tumours	Sex cord-stromal tumors	Germ cell tumors
Serous	Granulosa Cell Tumors	Teratomas
Endometrioid	Thecomas	Dysgerminomas
Clear Cell	Fibroma	Embryonal carcinoma
Mucinous	Leydig cell tumor	Non-gestational choriocarcinoma
Brenner (Transitional Cell)	Seroli Cell tumor	Struma Ovarii
Mixed Epithelial Tumours		Endodermal sinus tumor
Undifferentiated		
Unclassified		

women with high-grade tumours [10, 11]. In recent years, accumulating evidence has shown that the majority of high-grade serous ovarian and peritoneal tumours originate in the fimbria of the fallopian tube (serous tubal intraepithelial carcinoma). These malignant cells then metastasise to the ovaries and the peritoneal cavity [15, 16].

Endometrioid ovarian cancers are usually early stage (stage 1) and low grade.

Endometriotic cysts are possibly precursor lesions to endometrioid ovarian cancer. The presence of ARID1A mutations in endometriotic cysts and in endometrioid ovarian cancer suggests this cause relationship [12].

Clear-cell cancers incidence varies worldwide. It is more common among Japanese women. The prognosis for its stage 1 is relatively good. However, advanced stage clear-cell cancers have a worse prognosis than serous OC and the first tend to be resistant to the standard chemotherapeutic agents used. Clear-cell cancers are also strongly associated with endometriosis because a significant proportion carry ARID1A mutations [12].

Mucinous carcinoma usually present as large pelvic abdominoidal cystic masses suggesting mucinous histology. These tumors usually occurs in young adult women and are diagnosed in recent stages, having a good prognosis (5 years OS 80–90%) [85].

Malignant Brenner tumor (MBT) is extremely rare [43, 44]. Histologically MBTs demonstrate transitional- type differentiation as is seen in bladder and ureters with clear stromal invasion. But these tumors do not originate in the urothelial tract. It derive from sites of transitional cell metaplasia from ovarian surface epithelium. [45–47].

When more than one histological type are present in the histological analysis of an ovarian tumor and the minor component forms >10% this tumor is classified as mixed carcinoma. Undifferentiated carcinoma is rare and is likely to represent one end of the high-grade serous spectrum [13].

Malignant germ cell tumors (MGCT) (less than 5%), and sex cord-stromal tumors (SCST) (5–8%) are classified as non-epithelial ovarian cancer (NEOC), which mostly affect the adolescent, median 16–20 years, and present in early stages (85% stage 1). Germ cell tumor are the most common ovarian tumors in this age group. Fertility-sparing surgery is possible for both. The 5-year overall survival of MGCT and SCST can reach 75–100% and 97.2%, respectively [48].

Borderline tumours have low malignant potential. They comprise about 10–15% of ovarian tumours and do not fit into the category of benign or malignant. As most ovarian tumours are serous in origin. They are managed primarily by surgery and respond poorly to chemotherapy [59].

### 22.3 Diagnosis and Staging

A full clinical assessment is the first step to begin the diagnostic propaedeutics of the patient with suspected OC. However, women with early OC have few or no symptoms, making clinical diagnosis more difficult. Symptoms are most commonly seen with advanced disease. Abdominal or pelvic pain, nausea, anorexia, dyspepsia, constipation, diarrhoea, urinary frequency, vaginal bleeding, abdominal distension, fatigue, bloating, ascites and abdominal masses are the symptom referred by patients with OC [49, 51, 52].

Following imaging investigation and appropriate laboratory studies are recommended. Abdominal/pelvic ultrasound and measurement of serum CA 125 is routinely used to aid diagnosis. Others tumor markers can be measured if clinically indicated to assess NEOC. For example, alpha-fetoprotein (AFP) levels should be measured to assess for germ cell tumors in women younger than 35 years with a pelvic mass [54, 55]. Serum carcinoembryonic antigen (CEA) and CA 19–9 levels are measured when it is unclear whether an ovarian mass is of gastrointestinal origin, or a primary mucinous ovarian tumour. In these situations, colonoscopy and/or gastroscopy are considered, particularly when CA 125/CEA ratio is  $\leq 25$  [17, 50, 52].

In image exams the presence of a large lesion, multi-locular cysts, solid papillary projections, irregular internal septations and ascites are highly suggestive of ovarian cancer. A ‘risk of malignancy’ index can be calculated from clinical factors, ultrasound and CA 125. Computed tomography (CT) scans are routinely used to determine the extent of disease and to aid in surgical planning. Imaging of the chest with CT or chest X-ray should be done if respiratory symptoms are present. Magnetic resonance imaging (MRI) scans do not form part of routine investigations, but for lesions indeterminate on ultrasound, MRI increases the specificity of imaging evaluation, thus decreasing benign resections. Although 18F-FDG-avid ovarian lesions in postmenopausal women are considered suspicious for malignancy, PET/CT is not recommended for primary cancer detection because of high false-positive rates [53, 56, 59].

The diagnosis of OC is confirmed after pathologic analysis of a biopsy or surgical specimen, which may occur preoperatively, intraoperatively or postoperatively. Primary surgery remains the most common and preferred approach, but where this is deemed not feasible, an imageguided or laparoscopic biopsy should be carried out. Preoperative assessment with cross-sectional imaging (CT) is essential as it guides surgery and the pathway of intervention [59]. After confirming the diagnosis, genetic testing is recommended for all women with OC [39, 61].

**Table 22.2** FIGO staging

Stage I	Tumor limited to the ovaries
IA	Tumor limited to one ovary; no ascites or peritoneal washings containing malignant cells. No tumour on the external surface; capsule intact
IB	Tumor limited to both ovaries; no ascites or peritoneal washings containing malignant cells. No tumour on the external surface; capsule intact
IC	Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites
	IC1 Surgical spill
	IC2 Capsule rupture before surgery or tumor on ovarian surface
	IC3 Malignant cells in the ascites or peritoneal washings
<b>Stage II</b>	Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim)
IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic tissues
<b>Stage III</b>	Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA	Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)
	IIIA1 Positive retroperitoneal lymph nodes only
	IIIA1(i) Metastasis $\leq$ 10 mm
	IIIA1(ii) Metastasis $>$ 10 mm
	IIIA2 Microscopic, extrapelvic (above the brim) peritoneal involvement $\pm$ positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastasis $\leq$ 2 cm $\pm$ positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IIIC	Macroscopic, extrapelvic, peritoneal metastasis $>$ 2 cm $\pm$ positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
Stage IV	Distant metastasis excluding peritoneal metastasis
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Staging of ovarian cancer is surgical and the International Federation of Gynecology and Obstetrics (FIGO) staging (Table 22.2) remains the most powerful indicator of prognosis.

## 22.4 Treatment Plan

Primary treatment for presumed OC consists of surgery with an availability of a frozen section to identify a malignant specimen and appropriate surgical staging and debulking surgery, followed in most patients by systemic chemotherapy [57–60].

### ***22.4.1 Surgical Management of Early Primary Disease***

The aim of surgery for early OC is to resect the tumour and to undertake adequate staging. This initial non-fertility-sparing surgery should include aspiration of ascites or peritoneal lavage taken before manipulation of the tumour for peritoneal cytologic examinations, a total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) with every effort to keep an encapsulated mass intact during removal, omentectomy, multiple peritoneal biopsies of all abdominal fields and pelvic and para-aortic lymph node dissection up to the renal veins [59, 67]. If suspected or confirmed mucinous histology, appendectomy also should always be performed [85].

When young women are affected, fertility-sparing surgery (unilateral salpingo-oophorectomy or BSO preserving the uterus) could be considered in early-stage disease (IA or stage IC) and favourable histology (grade 1 or 2 borderline, mucinous, serous, endometrioid, germ cell, sex cord-stromal tumours), but in combination with complete surgical staging, thoroughly informing the patient about the potential risks and about completion surgery should be considered after finishing childbearing [22]. In some cases of pediatric/adolescent patients with clinically apparent early stage MGCT surgical staging may be omitted [84].

Although there is a trend for improved progression-free survival (PFS) and overall survival (OS) in the lymphadenectomy group when compared with the control group, the studies lacked the statistical power to be conclusive in this respect [21]. Depending on the histological grade and subtype, 15–30% of the patients with apparently early epithelial ovarian cancer (EOC) will be upstaged after comprehensive surgical staging [18–20]. Therefore, accurate surgical staging is important as it may unmask occult advanced disease.

### ***22.4.2 Surgical Management of Primary Advanced Ovarian cancer***

Debulking surgery is the initial treatment for patients with EOC clinical stages II, III, or IV and also to many of the malignant NEOT [23, 57, 59, 68, 69]. The aim is complete cytoreduction of all macroscopic visible disease or to less than 1-cm residual disease (optimal cytoreduction). To achieve this, for patients who can tolerate a large surgery, maximal surgical effort is required, including, if necessary, appendectomy, intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky pelvic and para-aortic lymph nodes, splenectomy, cholecystectomy, partial, hepatectomy, partial gastrectomy, partial cystectomy and/or distal pancreatectomy [59, 70, 71]. This has been shown to be associated with a significantly increased OS and PFS [23–25]. Residual tumour is a more powerful prognostic determinant than FIGO stage; patients with suboptimally debulked stage IIB–IIIB tumours had a

worse outcome than those with completely debulked stage IIIC tumours [23]. Debulking surgery is most widely performed via laparotomy, but, in select patients, minimally invasive procedures may be used to assess whether optimal cytoreduction is feasible reducing the number of futile laparotomies [67, 72–74].

The value of systematic pelvic and para-aortic lymphadenectomy in advanced disease has been widely discussed in recent years. A retrospective analysis of more than 1900 patients found that lymphadenectomy was associated with a prolonged survival in patients with no gross residual disease [27]. However, a prospective randomised trial of lymphadenectomy versus removal of bulky nodes in patients with <2 cm residual tumour showed an improvement in PFS but not OS for the lymphadenectomy group [28]. A large multi-centre, prospectively randomised trial including patients with newly diagnosed advanced OC (AOC) FIGO IIB-IV with macroscopic complete resection and pre- and intra-operatively clinical negative lymph nodes were randomized intra-operatively to systematic pelvic and para-aortic lymphadenectomy versus no systematic lymphadenectomy. Systematic pelvic and para-aortic lymphadenectomy (LNE) neither improve overall nor progression-free survival despite detecting and removing sub-clinical retroperitoneal lymph node (LN) metastases in 56% of the patients. Therefore, this trial indicated that systematic LNE of clinical negative LN in patients with AOC and complete resection should be omitted to reduce post-operative morbidity and mortality, just the removal of bulky lymph nodes is carried out as part of an attempt to achieve maximum cytoreduction [26].

In the therapeutic management of AOC, the best outcomes are consistently seen with complete resection of all visible disease (resection R0) and subsequently intra-peritoneal [78] or intravenous therapy, but a large prospective trial showed that in OC bulky stage IIIC or IV disease, three cycles of platinum-based neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy [25, 54, 64, 65]. As a result of these data, the use of primary chemotherapy with interval surgery is becoming more widely accepted and is offered to patients with poor performance status at presentation and in those an optimal cytoreduction will not be achieved [25, 75–77].

A prospective, non-randomized, multicenter trial of patients who underwent primary debulking for stage III–IV epithelial OC was realized with objective to assess preoperative predictive criteria of gross residual disease (RD) at primary cytoreduction in AOC. Three clinical and 8 radiologic criteria were significantly associated with the presence of any RD: age  $\geq 60$  years; CA-125  $\geq 600$  U/mL; ASA 3–4; lesions in the root of the superior mesenteric artery, splenic hilum/ligaments, lesser sac  $\geq 1$  cm, gastrohepatic ligament/porta hepatis, gallbladder fossa/intersegmental; suprarenal retroperitoneal lymph nodes; small bowel adhesions/thickening; and moderate-severe ascites. A ‘predictive score’ was assigned to each criterion and the rate of having any RD for patients who had a total score of 0–2, 3–5, 6–8, and  $\geq 9$  was 45%, 68%, 87%, and 96%, respectively. This model may be helpful in treatment planning [79].

### **22.4.3 Systemic Therapy**

#### **22.4.3.1 Adjuvant Chemotherapy for Early-Stage Disease**

In those patients with early-stage OC, but with high risk of recurrence (stage 1B/C grade 2/3, any grade 3 or clear-cell histology) the meta-analyses showed that chemotherapy is more beneficial than observation. Patients who received platinum-based adjuvant chemotherapy had better OS than patients who did not receive adjuvant treatment [33, 34]. The optimal duration of single-agent carboplatin or addition of paclitaxel for patients with early-stage disease remains controversial. There is a randomised trial (GOG 157) which showed that six cycles of carboplatin and paclitaxel were not associated with longer PFS or OS, but with a significantly greater toxicity than with three cycles [35] and there are no data to demonstrate that the addition of paclitaxel to carboplatin is superior. Therefore, it is reasonable to consider single-agent carboplatin to all women with intermediate and high-risk stage I disease for 3–6 cycles [59].

Surgical treatment alone and observation after is recommended just for patients with surgically staged IA or IB, grade 1 endometrioid carcinomas and other histologies, because in these cases the survival is greater than 90% [33, 82, 83].

#### **22.4.3.2 Neoadjuvant Chemotherapy**

When indicated, before neoadjuvant chemotherapy, histologic confirmation of OC should be obtained. Minimally invasive techniques maybe used to realize the biopsy. Intravenous taxane/carboplatin and liposomal doxorubicina/carboplatin are the regimens recommended for neoadjuvant and adjuvant therapy after interval debulking surgery. In addition, further studies have shown promising data with the use of bevacizumab in addition to standard neoadjuvant chemotherapy and the use of intraperitoneal chemotherapy as adjuvant treatment option for interval surgery [80, 81].

In general, 3 cycles of neoadjuvant chemotherapy are recommended before interval debulking surgery and 3 cycles after completing a minimum of 6 cycles of treatment. However, the patients should be evaluated for potential interval debulking surgery. This surgical procedure should be similar to those recommended for a primary debulking procedure. For patients with disease considered unresectable in evaluation for interval debulking surgery, this procedure may be performed after 4–6 cycles based on the clinical judgement.

#### **22.4.3.3 Chemotherapy for OC FIGO Stage II–IV**

Due to the risk of recurrence, for FIGO stage II–IV disease chemotherapy is recommended for all these patients post surgery. A combination of paclitaxel 175 mg/m<sup>2</sup> and carboplatin dosed at an area under the curve (AUC) of 5–6, both administered



intravenously on day 1 every 3 weeks usually for six cycles is the regimen more accepted by a consensus for EOC and some NEOC [36–38]. This regimen is associated with sensory peripheral neuropathy. There is no evidence to suggest that more than six cycles results in a better outcome.

The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer. For those patients who do not tolerate paclitaxel, docetaxel plus carboplatin or pegylated liposomal doxorubicin (PLD) plus carboplatin can be considered an alternative, based on two randomised clinical trials that showed similar efficacy [40, 41]. Docetaxel/carboplatin regimen is associated with increased risk for neutropenia and PLD/carboplatin, with more hematologic adverse events.

An alternative scheme with intraperitoneal (IP) and intravenous (IV) chemotherapy has been increasingly studied. Intraperitoneal chemotherapy has a solid pharmacokinetic background and consists of administration of part of the chemotherapy, usually the platinum agent, directly into the peritoneal cavity through a catheter. One randomised clinical trial with stage III OC with no residual mass greater than 1.0 cm demonstrated a benefit in PFS and OS for a regimen that included not only intraperitoneal cisplatin on day 2 and intravenous paclitaxel on day 1, but also intraperitoneal paclitaxel on day 8 every 3 weeks for six cycles. Grade 3 and 4 pain, fatigue, and hematologic, gastrointestinal, metabolic, and neurologic toxic effects were more common in the intraperitoneal-therapy group than in the intravenous-therapy group and only 42% of the patients in the intraperitoneal-therapy group completed six cycles of the assigned therapy. Quality of life was significantly worse in the intraperitoneal-therapy group before cycle 4 and three to 6 weeks after treatment but not 1 year after treatment [42]. Other studies, including a meta-analysis of five clinical trials confirmed a benefit for IP chemotherapy in OS [43, 63].

Intraperitoneal therapy has been seen more consistently considered in patients with FIGO stage III disease, with small volume (<1 cm) or no residual disease after surgery and with a appropriated performance status [39]. However, this treatment has not been adopted as a standard of care in the majority of institutions and countries due to its greater toxicity and difficulty in delivering all of the planned treatment. This has further influenced many clinicians still regard IP therapy as experimental [59].

For MGCT the most recommended chemotherapy regimen is different. It is based on bleomycin/etoposide/cisplatin (BEP) for 3–4 cycles postoperative for any stage embryonal tumors or endodermal sinus tumors, stages II to IV dysgerminoma and stage I, grade 2 or 3, or stage II to IV immature teratoma [39].

#### 22.4.3.4 Targeted Therapies

Angiogenesis has been a promising target in advanced EOC. The addition of the antiangiogenesis agent bevacizumab to front-line treatment (carboplatin and paclitaxel) showed a increased in PFS when compared with chemotherapy alone in two trials, GOG 218 and ICON-7 trials [62, 66]. The addition of bevacizumab to upfront chemotherapy has been approved in Europe but remains controversial in the United States [39, 61].

Olaparib, a poly ADP-ribose polymerase (PARP) inhibitor, was approved for patients with germline BRCA-mutated advanced ovarian cancer after three or more lines of chemotherapy based on overall response rate of 34% [39, 61].

## 22.5 Follow-Up

After the primary treatment, patients with EOC and some NEOC who have had a complete response should be seen every 3–6 months for 5 years and physically examined, mainly pelvic exam. They should perform imaging exams when clinically indicated. CA-125 and other tumor markers should be dosed if initially elevated [39].

## 22.6 Surgical Management of Relapsed Ovarian Cancer

Improved survival following secondary surgery is controversial [24, 29]. A secondary cytoreduction appears to be associated with a survival benefit only when a complete tumour resection can be obtained [30, 31]. This procedure can be considered when the recurrence occurs after 6–12 months after completion of initial chemotherapy, a complete resection was possible at first surgery, there is good performance status, there is not ascites and when a disease is localized and a complete tumour resection can be obtained [39, 59].

The value of a third cytoreduction surgery at later relapse is less clear. The largest multi-centre retrospective analysis showed that residual tumours retain a positive effect on survival even in the tertiary setting of epithelial ovarian cancer, attenuating the impact of other well-established negative prognostic predictors of survival such as ascites, advanced FIGO stage and peritoneal carcinomatosis [32].

## 22.7 Recurrent Disease

In the relapse setting, treatment considerations include the disease-free interval, existing toxicities from first-line treatment and volume of disease at the time of relapse. For patients whose disease recurs in less than 6 months, it is considered platinum-resistant and has a poor prognosis. For these patients, a nonplatinum agent (example: docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin), with or without bevacizumab, is indicated, but sequential single agent is most commonly used. For those with platinum-sensitive (recurrence beyond 6 months), a combination platinum-based chemotherapy, with or without bevacizumab, is indicated [39, 61].

### Questions

1. Where does the most common ovarian cancer occur?

- A. On tissue within the ovary
- B. On the surface of the ovarian tissue
- C. In egg-forming germ cells within the ovary
- D. Any of above

Answer: B – Introduction and Epidemiology: “More than 90% of malignant ovarian tumors are of epithelial origin, 5–6% of tumors constitute sex cord-stromal tumors, and 2–3% are germ cell tumors [7].”

2. Which of the following affirmative is correct about ovarian cancer?

- A. The majority of ovarian cancers are diagnosed late.
- B. Ovarian cancer is the third most common type of cancer in women.
- C. The overall 5-year relative survival rate has seen an important increase due the news chemotherapy drugs.
- D. The overall 5-year relative survival rate is more than 50%.

Answer: A – Introduction and Epidemiology: “Ovarian cancer (OC) is the fifth most common type of cancer in women...”

“The overall 5-year relative survival rate has seen only very modest increases (2–4%) since 1995 [3]. Currently this rate is between 30–40% across the globe. However, the disease typically presents at late stage when the 5-year relative survival rate is only 29%.”

3. Who is most at risk for developing ovarian cancer?

- A. A woman who has had multiple children
- B. A woman who use contraceptive pill
- C. A woman over the age of 60
- D. A woman of childbearing age

Answer: C – Introduction and Epidemiology: “This disease is predominantly in older, postmenopausal women (> 80% over 50 years).”

“In relation to reproductive history, women who have had multiple pregnancies have a lower risk than those with fewer pregnancies, who in turn have a lower risk than nulliparous women.”

“Use of the oral contraceptive pill, tubal ligation, breastfeeding and suppression of ovulation offer protection against OC.”

4. Which of the following affirmative is wrong about ovarian cancer?

- A. Ovarian cancer can occur at any age, even in childhood.
- B. Ovarian cancer is most common after menopause.
- C. Ovarian cancer affecting both ovaries is classified in stage 1
- D. Ovarian cancer with malignant cells in the ascites is classified in stage 3

Answer: D – “Table 22.2 -FIGO staging”.

5. Usually, the first treatment for ovarian cancer is...
- A. Surgery
  - B. Chemotherapy
  - C. Radiation
  - D. Any of the above

Answer: A – Treatment Plan. “Primary treatment for presumed OC consists of surgery with an availability of a frozen section to identify a malignant specimen and appropriate surgical staging and debulking surgery, followed in most patients by systemic chemotherapy.”

6. Which of the following affirmative is wrong about ovarian cancer?
- A. Ovarian cancer can be prevented.
  - B. Ovarian cancer can cause vaginal bleeding.
  - C. Ovarian cancer can affect both ovaries.
  - D. Ovarian cancer with malignant cells in the ascites is classified in stage 1C.

Answer: A – Diagnosis and Staging “... vaginal bleeding, abdominal distension, fatigue, bloating, ascites and abdominal masses are the symptom referred by patients with OC.”

“Table 22.2 -FIGO staging”

7. What is the most used tumor marker in the propaedeutics of ovarian cancer?
- A. Alpha-fetoprotein
  - B. CEA
  - C. CA 19-9
  - D. CA-125

Answer: D – Diagnosis and Staging “Abdominal/pelvic ultrasound and measurement of serum CA 125 is routinely used to aid diagnosis.”

8. Woman of 65 years with pelvic mass on physical examination. What tests should be required for this patient to evaluate ovarian cancer?
- A. Magnetic resonance imaging and CA-125
  - B. Computed tomography, CA-125, CEA, AFP
  - C. PET-CT, CA-125, CEA
  - D. Abdominal/pelvic ultrasound, CA-125

Answer: D – Diagnosis and Staging “Abdominal/pelvic ultrasound and measurement of serum CA 125 is routinely used to aid diagnosis. ... alpha-fetoprotein (AFP) levels should be measured to assess for germ cell tumors in women younger than 35 years with a pelvic mass [54, 55]. Serum carcinoembryonic antigen (CEA) and CA 19–9 levels are measured when it is unclear whether an ovarian mass is of gastrointestinal origin, or a primary mucinous ovarian tumour. ... Magnetic resonance imaging (MRI) scans do not form part of routine investigations... Although 18F-FDG-avid ovarian lesions in postmenopausal women

are considered suspicious for malignancy, PET/CT is not recommended for primary cancer detection because of high false-positive rates”.

9. Woman with pelvic mass on physical examination. When should we think about germ cell tumor?
- women younger than 35 years with increased AFP
  - women over 45 years with increased AFP
  - women younger than 35 years with increased CA-125
  - women over 45 years with increased CA-125

Answer: A – Diagnosis and Staging “...alpha-fetoprotein (AFP) levels should be measured to assess for germ cell tumors in women younger than 35 years with a pelvic mass [54, 55].”

10. Staging of ovarian cancer is done by means of...
- Surgery
  - Abdominal/pelvic Computed tomography, chest X-ray and CA-125
  - Abdominal/pelvic magnetic resonance imaging and CA-125
  - Abdominal/pelvic ultrasound, PET-CT, CA-125

Answer: A – Diagnosis and Staging “Staging of ovarian cancer is surgical...”

11. An 62-year-old female was diagnosed with ovarian cancer. Following gynecological surgery, pathological evaluation showed stage IIIC epithelial ovarian cancer. What is the most appropriate adjuvant therapy?
- Adjuvant therapy is not necessary
  - Six cycles of chemotherapy combined with intravenous paclitaxel and carboplatin
  - Three cycles of chemotherapy combined with intravenous paclitaxel and carboplatin
  - Chemotherapy combined with Radiotherapy

Answer: B – Chemotherapy for OC FIGO stage II–IV: “Due to the risk of recurrence, for FIGO stage II–IV disease chemotherapy is recommended for all these patients post surgery. A combination of paclitaxel 175 mg/m<sup>2</sup> and carboplatin ... both administered intravenously ... for six cycles is the regimen more accepted by a consensus for EOC.”

12. An 73-year-old female was diagnosed with pelvic mass on physical examination. Following gynecological surgery, pathological evaluation showed stage IA clear cell ovarian cancer. What is the most appropriate adjuvant therapy?
- Adjuvant therapy is not necessary
  - Six cycles of chemotherapy combined with intravenous paclitaxel and carboplatin
  - Three cycles of chemotherapy combined with intravenous paclitaxel and carboplatin

#### D. Chemotherapy combined with Radiotherapy

Answer: A – Adjuvant chemotherapy for early-stage disease: “Surgical treatment alone and observation after is recommended just for patients with surgically staged IA or IB, grade 1 endometrioid carcinomas and other histologies, because in these cases the survival is greater than 90%.”

13. An 30-year-old female was diagnosed with pelvic mass on physical examination. The patient does not have children and wishes to preserve fertility. In what situations can not a fertility-sparing surgery be proposed for this patient?

- A. stage IA clear cell, grade 1 ovarian cancer
- B. stage IC mucinous ovarian cancer
- C. stage IA germ cell grade 2 ovarian cancer
- D. stage IC sex cord-stromal grade 2 tumours ovarian cancer

Answer: A – Surgical management of early primary disease: “When young women are affected, fertility-sparing surgery ( unilateral salpingo-oophorectomy or BSO preserving the uterus) could be considered in early-stage disease (IA or stage IC) and favourable histology (grade 1 or 2 borderline, mucinous, serous, endometrioid, germ cell, sex cord-stromal tumours), but in combination with complete surgical staging.”

14. A 40-year-old female patient who was unable to have children made the choice to undergo in-vitro fertilization (IVF). The patient’s ovaries were super stimulated by chemicals to help ovulation occur. After each cycle an ultrasound was performed. After the third cycle of IVF the patient developed a right complex ovarian cyst with irregular mural projections and internal vascularity. The patient wished to continue with IVF treatments, therefore a conservative surgery was proposed. A right laparoscopy salpingo-oophorectomy was performed and an invasive endometrioid adenocarcinoma restricted to ovary was identified by frozen section. What is the most appropriate surgery in this case?

- A. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields, pelvic and para-aortic lymph node dissection and appendectomy
- B. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields, pelvic and para-aortic lymph node dissection without appendectomy
- C. A unilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields, pelvic and para-aortic lymph node dissection without appendectomy
- D. A unilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies of all abdominal fields and appendectomy

Answer: C – Surgical management of early primary disease: “When young women are affected, fertility-sparing surgery (unilateral salpingo-oophorectomy or BSO preserving the uterus) could be considered in early-stage disease (IA or stage IC)

and favourable histology (grade 1 or 2 borderline, mucinous, serous, endometrioid, germ cell, sex cord-stromal tumours), but in combination with complete surgical staging.”

15. A 16 year old girl with pelvic pain was diagnosed with pelvic mass on physical examination. A 7cm ovarian tumor was visualized on abdominal/pelvic ultrasonography. What is the most suitable histological type?
- A. Serous
  - B. Mucinous
  - C. Clear Cell
  - D. Dysgerminoma

Answer: D – Pathology: “Malignant germ cell tumors (MGCT) (less than 5%), and sex cord-stromal tumors (SCST) (5–8%) are classified as non-epithelial ovarian cancer (NEOC), which mostly affect the adolescent, median 16–20 years”.

### **Fictitious Clinical Case**

Ms. Catarina Brasil, 52 years old, natural from Porto, Portugal presented with increased abdominal volume 2 months ago, dyspepsia, flank pain and weight loss performed ultrasonography that showed ascites and abdominal mass. At medical consultation was requested CA-125: 325 U/ml and abdominal/pelvic CT that showed: ascites, expansive solid-cystic formation of 15 cm in the central region of the abdomen and pelvis on the right, 3 expansive formations in the pelvis measuring 6.5 cm, 8 cm and 4.5 cm each. Patient without comorbidities. Faced with the suspicion of ovarian cancer, the gynecological oncology surgeon decided to exploratory laparotomy with optimal cytoreduction surgery intensity. During the procedure was detected large amount of ascites, 5 cm right ovary mass, 5 cm retrouterine mass, 15 cm tumor mass in omento, right subdiaphragmatic implant of 3 cm and lesions suggestive of metastatic implantation affecting 3 points of the intestine, vesical peritoneum, hepatic round ligament, right and left flank peritoneum. Abdominal total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, resection of retrouterine and peritoneal masses, intestinal implants and of bulky nodes were performed. All evidence of macroscopic disease was removed. Pathological assessment showed serous high grade ovarian cancer. Following surgery, the patient’s CA-125 levels declined to 81 U/ml. After 1 month the patient received six cycles of conventional treatment. During chemotherapy, the patient presented neutropenia grade 2 and distal paraesthesia grade 1. Following chemotherapy, CA-125 levels declined to 7.3 U/ml and abdominal/pelvic CT showed no disease.

- (a) Which classification should be used for patient staging above?

The International Federation of Gynecology and Obstetrics (FIGO) staging. Stage IIIC – Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes. Macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

(b) Which chemotherapy regimen is most commonly accepted for this patient?

A combination of paclitaxel 175 mg/m<sup>2</sup> and carboplatin dosed at an area under the curve of 5–6, both administered intravenously on day 1 every 3 weeks usually for six cycles.

(c) If in less than 6 months the patient has increased Ca-125 and ascites what should be the conduct?

Due to early relapse (less than 6 months), this disease is considered platinum-resistant and has a poor prognosis. For these patients, a nonplatinum agent (example: docetaxel, oral etoposide, gemcitabine, liposomal doxorubicin), with or without bevacizumab, is indicated.

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# Chapter 23

## Approach and Management of Cervical Cancer



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**Abstract** Cervical cancer (CC) represents the third most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide [GLOBOCAN: Estimated cancer incidence, mortality and prevalence worldwide in 2012 international agency for research on cancer; 2012. Available at: [http://globocan.iarc.fr/Pages/fact\\_sheets\\_population.aspx](http://globocan.iarc.fr/Pages/fact_sheets_population.aspx). Accessed 27 Dec 2017, 2012]. In 2012, across the world, 528,000 new cases were diagnosed with 266,000 deaths, with 85% of the cases occurring in developing countries (GLOBOCAN: Estimated cancer incidence, mortality and prevalence worldwide in 2012 international agency for research on cancer; 2012. Available at: [http://globocan.iarc.fr/Pages/fact\\_sheets\\_population](http://globocan.iarc.fr/Pages/fact_sheets_population).

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**Keywords** Cervical cancer · Chemotherapy · Radiotherapy

## 23.1 Introduction

Cervical cancer (CC) represents the third most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide [1]. In 2012, across the world, 528,000 new cases were diagnosed with 266,000 deaths, with 85% of the cases occurring in developing countries [1–3]. In the United States, it is the third most common gynaecologic cancer diagnosed and cause of death among gynaecologic cancers [4]. Human papillomavirus (HPV) is central to the development of cervical neoplasia and can be detected in 99.7% of CCs [5].

## 23.2 Epidemiology and Staging of Invasive Cervical Cancer

The incidence and mortality rates of CC are dependent upon screening programs; the most common strategy employed has been cytological screening using the Papanicolaou (PAP) smear test and HPV vaccination. Persistent HPV infections are necessary, although not sufficient to cause CC [5]. The introduction of HPV vaccines has impacted on CC control programs [6]. These interventions resulted in a 75% decrease in the incidence and mortality of CC over the past 50 years in developed countries [7].

Inequalities in the use of CC screening services due to socio-economic status reflects the widening disparities, with more deprived women less likely to be

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screened [8]. There is an inverse correlation between the incidence of CC and countries' Human Development Index (HDI). The difference in age-standardized incidence rate of low and very high HDI countries is of approximately three-fold and the corresponding mortality rates vary up to six-fold [1].

In the United States, overall rates of CC are decreasing although incidence remains high in Africa, Latin America and the Caribbean and Asia. Among a total of 266,000 CC deaths worldwide, 90% (233,000) occurred in these regions [1].

### ***23.2.1 Africa***

CC is the second most common cancer; the highest rates are in Eastern Africa. On the other hand, in Northern Africa where there is a predominance of Muslim population, CC is uncommon. Muslims are considered to have a more conservative sexual behaviour compared to other populations in sub-Saharan Africa or in western countries, and therefore the prevalence of HPV is low. The background prevalence of HPV infection in sub-Saharan Africa is high and it is estimated to be 24% on average (ranging from 3.2% in Sudan to 47.9% in Guinea). In addition, the screening programmes are scarce, hence increasing the risk for CC. High quality cancer registries and reliable mortality data are rare in Africa [9].

### ***23.2.2 Latin America and Caribbean***

CC is among the first five most common cancers in this region, both in terms of incidence and mortality. For example, in Brazil in 2018–2019, 16,370 new cases of invasive CC were estimated per year, a rate of 1543 cases per 100,000 Brazilian women, therefore ranking CC as the third most common cancer among women [10].

In this region, the lifetime risk of CC incidence is highest in Bolivia, 4.9% and Nicaragua, 3.5%, also the two countries with the highest mortality rates. Although the risk variations differ among populations, overall the estimated incidence is similar to the average for low HDI countries.

### ***23.2.3 Asia***

Similarly, in Asia CC is the third most commonly diagnosed cancer with an estimated 285,000 new cases and 144,000 deaths in 2012 [1]. There is a large heterogeneity in risk in the region. For example, in the most populated countries, India and China, the incidence rate of the latter is 3 times lower than the former. In addition, there is considerable regional variability within the two countries. Kazakhstan, Cambodia, Mongolia, Kyrgyzstan, Myanmar and Bangladesh also have an increased incidence of CC and the lifetime risk are estimated to be 2% or higher.

CC screening is crucial to detect initial changes and early stage disease since it is usually asymptomatic. The aim is to identify abnormal cells sampled from the transformation zone (junction of the ectocervix and endocervix), where cervical dysplasia and cancer generally arise [11]. There are two main types of CCs: squamous cell carcinoma that accounts for 80–90% of the cases and adenocarcinoma which represents 10–20% of CC histologies. There has been an increase in adenocarcinoma relative distribution compared with squamous cell carcinoma in developed countries. Adenocarcinoma has significantly lower survival rates compared with squamous cell carcinoma stage to stage, with higher distant failure rates [12].

The risk factors related with this pathology are mainly: early onset of sexual activity and early age of first birth (<20 years old), lifetime number of sexual partners, a high risk sexual partner (multiple partners or known HPV infection), history of sexually transmitted disease (STD) e.g. *Chlamydia trachomatis* and genital herpes, history of vulvar and/or vaginal squamous intraepithelial neoplasia (related to HPV infection) and immunosuppression (impairment to clear HPV infection). Other minor risk factors are oral contraceptive use, cigarette smoking and genetic alterations [13].

### 23.2.4 *Diagnosis and Staging*

The symptoms are usually absent or mild in early stage disease, such as discomfort with intercourse, spotting and vaginal watery discharge. In more advanced disease, symptoms such as urgency or urinary incontinence, constipation and severe pelvic pain may be present.

Colposcopy is an important diagnostic tool in uterine CC. It is performed when an abnormal screening test is observed and guides the biopsy in all suspected precancerous or cancerous lesions. Conization, which means an extirpation of the entire transformation zone, is necessary to diagnose microscopic disease (stage IA) with examination of the entire lesion. This procedure should also be done when normal colposcopy is seen and a suspected malignancy persists. All macroscopic suspected lesion should be biopsied, avoiding gross necrotic area since it could be non-diagnostic.

The system used for staging these patients is recommended by FIGO (updated in 2009 – Table 23.1) and is based in a thorough pelvic examination since non-invasive radiographic imaging may not be available in low resource countries [14]. FIGO system is intended to comparison purposes and not for guiding treatment. Pelvic examination should focus on the extend of disease in vaginal walls, parametrial, sidewall and uterosacral ligament and are best felt and described by rectovaginal examination. In patients with discomfort and pain during routine pelvic evaluation, an examination under anaesthesia should be done. Groin, femoral and scalene lymph node should also be evaluated. This system allows the following procedures for staging purposes: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous pyelography, ultrasound of the renal tract, and X-ray examination of the lungs and skeleton [14]. Blood tests should



**Table 23.1** FIGO Staging System 2009

TNM	Stage		
T1	I		The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
T1a		IA	Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm
T1a1		IA1	Measured invasion of stroma $\leq 3$ mm in depth and $\leq 7$ mm width
T1a2		IA2	Measured invasion of stroma $>3$ mm and $<5$ mm in depth and $\leq 7$ mm width
T1b		IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
T1b1		IB1	Clinical lesions no greater than 4 cm in size
T1b2		IB2	Clinical lesions $>4$ cm in size
T2	II		The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina
T2a		IIA	Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement
T2a1		IIA1	Clinically visible lesion $\leq 4$ cm
T2a2		IIA2	Clinically visible lesion $>4$ cm
T2b		IIB	Obvious parametrial involvement but not onto the pelvic sidewall
T3	III		The carcinoma has extended onto the pelvic sidewall. The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes
T3a		IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall
T3b		IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
T4	IV		The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum
T4		IVA	Spread to adjacent pelvic organs.
M1		IVB	Spread to distant organs

TNM classification by AAJC 8th Edition

T	N	M	
TX			Primary tumor cannot be assessed
T0			No evidence of primary tumor
T1			The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
T1a			Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm
T1a1			Measured invasion of stroma $\leq 3$ mm in depth and $\leq 7$ mm width

(continued)

**Table 23.1** (continued)

T1a2			Measured invasion of stroma >3 mm and <5 mm in depth and ≤7 mm width
T1b			Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
T1b1			Clinical lesions no greater than 4 cm in size
T1b2			Clinical lesions >4 cm in size
T2			The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina
T2a			Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement
T2a1			Clinically visible lesion ≤4 cm
T2a2			Clinically visible lesion >4 cm
T2b			Obvious parametrial involvement but not onto the pelvic sidewall
T3			The carcinoma has extended onto the pelvic sidewall. The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes
T3a			Involvement of the lower vagina but no extension onto pelvic sidewall
T3b			Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
T4			The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum
T4			Spread to adjacent pelvic organs.
	NX		Regional lymph nodes cannot be assessed
	N0		No regional lymph node metastasis
	N0(+)		Isolated tumor cells in regional lymph nodes no greater than 0.2 mm
	N1		Regional lymph node metastasis
		M0	No distant metastasis
		M1	Spread to distant organs (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant lymph nodes; lung, liver or bone)

include a complete blood count and renal and liver functions. Serologic tests for syphilis and HIV are recommended based on discussion with patient about the risks and benefits. Suspected bladder or rectal involvement should be confirmed by biopsy and the presence of bullous oedema should not permit to be allotted to stage IVA.

In centres where resources are available, imaging with MRI, CT scans or PET-CT may be of value when added to clinical assessment, allowing the identification of additional prognostic factors, such as lymph node status, and helping to achieve a better approach with extension of radiotherapy fields [15–18]. However, it is important to keep in mind that these exams do not alter FIGO staging system. Compared to MRI and CT scans, PET-CT seems to be better at identifying lymph node metastasis and distant disease [19, 20]. MRI may help in patients who desire to maintain fertility. The gold standard evaluation of lymph node status is the surgical node

dissection but it is an area of debate, since it did not show to improve outcomes [21, 22]. Despite of being controversial and not recommended as routine practice, surgical node staging of the para-aortic lymph nodes, preferable by minimally invasive surgeries, could be considered to assess metastatic disease and to tailor radiotherapy field.

Sentinel lymph node is gaining more acceptance in recent years and may be useful in patients with early stage disease to decrease pelvic lymphadenectomy [23–26]. Prospective studies have demonstrated the feasibility of this approach in early stage disease and suggest that full lymphadenectomy may be omitted [24, 25]. Sentinel lymph node sensitivity seems to be better in patients with tumors less than 2 cm and when ultrastaging protocol is used in these nodes the detection of micro-metastasis and isolated tumour cells increase [27–31]. Another advantage of SLN is the fact of identifying nodes in unusual location, which could be lost compared to standard pelvic lymphadenectomy. Two meta-analyses showed a high rate of SLN detection and sensitivity [32, 33]. Bilateral SLN detection provides a more reliable assessment of SLN compared to unilateral detection. Surgeons should keep in mind that adherence of SLN algorithm is important and perform a side specific lymphadenectomy when SLN is not mapped and also to resect all suspicious node, regardless of mapping [25].

The TNM nomenclature is appropriate in cases treated by surgical procedures where pathologist's findings can be the basis for an accurate extension of disease, but this should not change the clinical staging. Recently, in 2017, the TNM staging was updated by the American Joint Committee on Cancer (AJCC) in its 8th edition. The major updates were that N1 was removed from FIGO IIIB and para-aortic metastasis was removed from M1 in AJCC staging system.

### 23.3 Molecular Mechanisms

Human papillomavirus (HPV) is central to the development of cervical neoplasia and can be detected in 99.7% of cervical cancers [5]. It is the single most important etiological agent in CC, but the infection alone is insufficient for malignant transformation; rather, the virus provides host cells with additional growth stimuli, which extend the proliferative capacity of the infected cell. This implies that HPV oncogenes can override cellular control mechanisms, which in untransformed cells regulate cell cycle progression in response to various antiproliferative signals. Pathogenesis of CC is a multifactorial and multistage process, involving aberrant sequential expression of multiple sets of cellular and viral genes.

There are four major steps in CC development: infection of metaplastic epithelium at the cervical transformation zone, viral persistence, progression of persistently infected epithelium to cervical precancer, and invasion through the basement membrane of the epithelium [34].

HPV infection is a common sexually transmitted infection, which a majority of infected women are able to clear by mounting an effective immune response. Almost

50% of women will be infected within 4 years after the onset of sexual activity, with prevalence peaking between 25 and 35 years of age. Persistent infections and precancer are established, typically within 5–10 years, from less than 10% of new infections. Invasive cancer arises over many years, even decades, in a minority of women with precancer, with a peak or plateau in risk at about 35–55 years of age.

Each genotype of HPV acts as an independent infection, with differing carcinogenic risks linked to evolutionary species [34]. Over 40 types of HPV are known to infect the cervical mucosa, being either low-risk (including 6, 11, 40, 42, 54, and 57) or high-risk types (including 16, 18, 26, 31, 33, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68) for CC [35, 36].

HPV has a double-stranded circularized genome that can be divided into early (E1–E7) and late (L1, L2) open reading frames (ORF). High risk HPV genotypes code for three early proteins (E5, E6, and E7) with cellular growth-stimulating and transforming properties. In productive HPV infection, HPV DNA remains in an episomal state, and the E1/E2 ORFs repress expression of the 2 most important HPV oncoproteins, E6 and E7 [37]. In contrast, in CC, E1/E2 is frequently disrupted by integration of viral DNA into the host genome, resulting in upregulated overexpression of E6 and E7 [37, 38]. The overexpression of E6 promotes the degradation of the cell cycle regulatory protein p53 through the ubiquitin-mediated pathway, resulting in unchecked cellular progression [35]. By contrast, the E7 oncoprotein binds to and promotes the degradation of the retinoblastoma gene (Rb), resulting in disruption of the Rb cyclin/p16<sup>INK4a</sup> cell cycle regulatory pathway [39]. This results in continuous cell proliferation with the increasing risk of accumulation of DNA damage that eventually leads to cancer.

In CC, it has been demonstrated that HPV E6 oncoprotein regulates differentiation-associated genes. Santin et al. identified 240 genes that showed greater than two-fold up-regulation in CC compared with normal cervical mucosa [40]. Genes that showed the highest levels of differential overexpression in cervical cancer included p16<sup>INK4a</sup>, minichromosome maintenance proteins 2, 4, and 5, cyclin D1 prostaglandin E synthase, topoisomerase 2 alpha (TOP2a) and the E2F transcription factor 1. p16<sup>INK4a</sup>, a tumor suppressor protein and cyclin-dependent kinase inhibitor (CDK), acts as a tumor suppressor by blocking cdk4 and CDK6-mediated pRb phosphorylation, resulting in inhibition of E7-dependent transcription and inhibition of cell cycle progression at the G1 to S checkpoint [41]. The repression of p16<sup>INK4a</sup> gene expression by hypermethylation or mutation is common in cancer cell lines and primary human tumours. However, in most CC, the functional inactivation of pRb by HPV E7 results in reciprocal overexpression of p16<sup>INK4a</sup>, secondary to a negative feedback loop between pRb and p16<sup>INK4a</sup>. As reviewed by Dehn and co-workers, p16<sup>INK4a</sup> overexpression in cervical neoplasia is a surrogate marker of HPV E7-mediated pRb catabolism, indicating persistent infection with risk of development of CC. Immunohistochemical studies indicate that p16 is highly expressed in virtually 100% of squamous cell carcinomas but is rarely detected in benign squamous mucosa [42].

Modulation of growth-regulating nuclear proteins by binding of HPV oncoproteins is a necessary step in the carcinogenic process. HPV E7 protein regulates key modulators, such as signalling factors, cell cycle regulators, chaperones, and thus

escape immune surveillance [43]. Several nuclear growth-regulating proteins were shown to be targets for viral oncoproteins including p53, a cellular protein, bearing features of a tumor suppressor, which can block cell cycle progression in G1; under certain conditions, p53 induces apoptotic cell death and thereby helps to eliminate cells with damaged DNA. Several viral proteins, including the E6 protein of HPV-16, interact with p53. The pRb, and the related proteins p107 and p130, which share the ability to arrest mammalian cells in G1 with pRb, are targeted by several DNA tumour virus oncoproteins, including HPV-16 E7. These effects of E7 depend on the pRb binding domain of the viral protein. Apoptosis can be blocked by coexpression of E6 or the expression of E7 in a p53-null background. It was shown that E6 can also prevent p53-independent apoptosis, and the data suggest that the ability of E6/E7 to modulate the frequency of apoptosis may be part of the mechanism through which these genes contribute to carcinogenesis.

HPV may also impact with cell cycle interacting with critical signalling cascades. HPV oncoproteins were shown to intervene at specific points in various signalling cascades, giving rise to specific downstream signals, which mimic physiological activation of a given pathway. Alternatively cellular transcription factors, which under physiological conditions are activated indirectly through signal transduction, can be directly activated by the binding of viral oncoproteins without any intermediate signalling event required [44]. The HER family of receptor proteins plays a key role in tumorigenesis and disease progression. Immunohistochemical analyses have identified all members of the HER family in cervical neoplasia. EGFR is frequently overexpressed in HPV-associated dysplasias and carcinomas, implying that it is important for the progression of keratinocytes to malignancy. Around 80% of cervical squamous cell tumors express EGFR [45, 46] and cell lines from recurrent and metastatic sites of disease tend to express higher levels of EGFR when compared to those obtained from primary sites [46]. Arias-Pulido and co-investigators analysed 89 samples for EGFR mutations in exons 19–21 [47], and nine CC cell lines were evaluated for mutations in exons 18–21: no mutations were detected in any sample in either group. In a separate study, no amplification of the EGFR gene was detected [48]. HER2 is overexpressed strongly (3+) in 6% and moderately (2+) in 20% of the specimens and amplification of the gene (>4 copies) is observed in overall 21% with 80% of the 3+ (4/5) but only 19% of the 2+ (3/16) cases being positive [46]. Overexpression was also found in 74.4% for HER3 and in 79.5% for HER4 [46]. Survival analysis revealed a significant association of HER2 and HER3 overexpression with poor prognosis ( $p = 0.006$ ;  $p = 0.05$ , respectively), and most data also associates HER1 overexpression with poor outcome [49], although some controversies exist [46]. Since EGF and EGFR expression as well as EGFR signalling is known to be modulated during differentiation and transformation, it is tempting to speculate about the relevance of EGF-modulated E6/E7 expression for both, the viral life cycle and the HPV-induced carcinogenesis process.

Evidence of involvement of PI3K/AKT/mTOR signalling pathway in HPV cervical carcinogenesis has also been reported. HPV18 E6 variants are able to upregulate phospho-PI3K protein, strongly correlating with activated Mitogen-Activated Protein Kinase (MAPK) and cell proliferation [50]. In addition, the E7 oncoprotein

from HPV16 enhance both the cytoplasmic retention of p27 and the migration of human foreskin keratinocytes, positive regulators of cellular motility and markers of poor prognosis in several forms of cancer, in a PI3K/AKT-dependent manner [51]. E7 protein from HPV-16 can modulate the cytoplasmic localization of p27 and may in turn regulate tumour metastasis/aggressiveness through the PI3K/AKT pathway. Human papillomavirus virus-like particles (VLPs) are also able to activate the RAS/MAP kinase pathway and RAS can also elicit an anti-apoptotic signal via PI3-kinase. Binding of VLPs from HPV types 6b, 18, 31, 35 and BPV1 results in activation of PI3-kinase. Activation is achieved by either L1 or L1/L2 VLPs and is dependent on both VLP-cell interaction and correct conformation of the virus particle. VLP-induced PI3-kinase activity results in efficient downstream signaling to AKT. Bertelsen et al. have demonstrated that PI3K-AKT pathway is constitutively activated in CC, but PTEN mutation or loss of heterozygosity is not frequent [52, 53]. PTEN promoter methylation has been detected in up to 40% of cervical dysplasia patients and up to 58% of CC specimens [53]. Cheung et al. and Janku et al. investigated *PI3KCA* and MAPK pathway mutation status in patients with advanced breast and gynaecological (cervical, endometrial and ovarian) cancer and detected 18% of the tumours with *PI3KCA* mutations, being as high as 36% in CC. Patients harboring *PI3KCA* mutations and refractory to a median of two prior therapies were treated with PI3K/AKT/mTOR pathway inhibitors and a response rate of 30% was observed [54]. Chen *et al* studied 23 samples of normal cervical epithelium, 25 of low-grade squamous intraepithelial lesions, 19 high-grade squamous intraepithelial lesions and 31 squamous cell carcinomas. The expression of phospho-MAPK/ERK1/2 were strongly associated with cervical neoplastic progression [55]. VLPs are also able to activate the RAS/MAP kinase pathway. RAS can also elicit an anti-apoptotic signal via PI3-kinase, as described above. These data suggest that papillomaviruses use a common receptor that is able to signal through to RAS. Combined activation of the RAS/MAP kinase and PI3-kinase pathways may be beneficial for the virus by increasing cell numbers and producing an environment more conducive to infection [56].

Regarding angiogenesis, its early initiation, also named “angiogenic switch”, is essential for cancer survival and occurs when stimulatory factors overcome inhibitory factors promoting the formation of new blood vessels [57]. The activation of the vascular endothelial growth factor (VEGF) promotes intracellular signalling pathways that are responsible for vascular permeability, endothelial cell proliferation and migration, and stabilization of new blood vessels. HPV infection may promote the “angiogenic switch” – molecularly, the consequences of viral integration into host DNA activates a cascade through which the human papilloma viral oncoprotein E6 degrades the cellular tumor suppressor gene product p53, while the human papilloma viral oncoprotein E7 inactivates the tumor suppressor gene product retinoblastoma. This cascade ultimately leads to increased hypoxia-inducible factor alpha and increased VEGF production, which promotes angiogenesis [58]. Increased VEGF expression also correlated with higher stage, increased risk of lymphovascular space invasion, greater likelihood of parametrial spread, and lymph node metastasis [59]. Pathologically, a high microvessel intratumoral density of the endothelial cell antigen CD31 predicts a poor prognosis among women diagnosed with invasive CC.

## 23.4 Pathology

### 23.4.1 *Cervical Intraepithelial Neoplasia*

Many systems have been developed for classifying cervical cytologic findings. Although criteria for the diagnosis of CIN and degree of neoplasia vary somewhat between pathologists, the important features of CIN are cellular immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity. The term cervical intraepithelial neoplasia, as proposed by Richart [60] refers to a lesion that may progress to invasive carcinoma:

CIN 1 – Mitoses and immature cells present only in the lower third of the epithelium;

CIN 2 – Lesions involving only the lower and middle thirds of the epithelium;

CIN 3 – Lesions involving the upper third of the epithelium.

### 23.4.2 *Comparison of Cytology Classification Systems for Cervical Neoplasms*

Following a 1988 National Cancer Institute Consensus Conference, the Bethesda system of classification was developed in an effort to further standardize reporting [61]. This system defines squamous intraepithelial lesions (SILs) as including all squamous alterations in the cervical transformation zone that are induced by HPV; SILs include all lesions that were classified in previous systems as condyloma, dysplasia, or CIN. The Bethesda system divides SILs into two groups: low grade and high grade. Low-grade SILs (LSILs) have nuclear crowding or atypia without frequent mitoses, parabasal cell anisokaryosis, or coarse chromatin; these lesions are usually associated with low-risk HPV types and have a low likelihood of progressing to invasive cancers. High-grade SILs (HSILs) have nuclear atypia in lower and upper epithelial layers, abnormal mitoses, coarse chromatin, and loss of polarity. HSILs are usually associated with high-risk HPV types and have a higher likelihood of progressing to invasive cancer. The Bethesda system was meant to replace the Papanicolaou system and is now widely used in the United States. However, its use is still controversial. Some groups [62, 63] argue that the new nomenclature has failed to improve diagnostic accuracy and believe that with dichotomization of the spectrum of atypical lesions, lesions that were formerly classified as CIN 2 (now HSIL) may be overtreated despite their relatively low risk of progression.

The term atypical squamous cells of undetermined significance (ASCUS) was introduced by Bethesda system. This uncertain diagnosis is now the most common abnormal Pap smear result in United States laboratories [64], with 1.6–9% of Pap smears reported as having ASCUS. Although most cases of ASCUS reflect a benign process, about 5–10% are associated with an underlying HSIL, and one-third or more of HSILs are heralded by a finding of ASCUS on a Pap smear.

Histopathologic types of CC are [65]: squamous cell carcinoma (69%), adenocarcinoma (including adenosquamous – 25%) and other histologies (6%). The incidence of invasive cervical adenocarcinoma and its variants has increased dramatically over the past few decades, particularly in younger women [66, 67]. Several causative factors have been proposed to explain this trend, including increased prevalence of specific HPV-16 and 18 variants that are associated more with adenocarcinoma than with squamous cell carcinoma as well as exposure to oestrogens, both endogenous (e.g., obesity) and exogenous (e.g., hormonal contraception, postmenopausal oestrogen therapy). Adenosquamous tumors exhibit both glandular and squamous differentiation. They may be associated with a poorer outcome than squamous cell cancers or adenocarcinomas [12].

Neuroendocrine or small cell carcinomas can originate in the cervix in women, but are infrequent [68]. Rhabdomyosarcoma of the cervix is rare; it typically occurs in adolescents and young women [69]. Primary cervical lymphoma and cervical sarcoma are also rare [70, 71].

### **23.4.3 Adenocarcinoma In Situ**

Adenocarcinoma in situ (AIS) is diagnosed when normal endocervical gland cells are replaced by tall, irregular columnar cells with stratified, hyperchromatic nuclei and increased mitotic activity but the normal branching pattern of the endocervical glands is maintained and there is no obvious stromal invasion. About 20–50% of women with cervical AIS also have squamous CIN [72]. Because AIS is frequently multifocal, cone biopsy margins are unreliable. AIS is a precursor of invasive adenocarcinoma. It is found adjacent to many invasive adenocarcinomas, often accompanied by squamous dysplasia. Both AIS and invasive adenocarcinoma of the cervix are associated with HPV (usually type 18, but sometimes type 16). AIS is characterized by preservation of the overall endocervical gland architecture. However, endocervical glands and surface epithelium are replaced to varying degrees by cells displaying atypia, including nuclear enlargement and stratification, nuclear hyperchromasia, and mitotic figures. Most adenocarcinomas in situ occur near the transformation zone, and skip lesions are unusual [72].

### **23.4.4 Squamous Cell Carcinoma**

Around 80–90% of CC are squamous cell carcinomas. Squamous carcinoma of the cervix includes both microinvasive squamous carcinoma and more deeply invasive carcinoma. Small cell squamous carcinomas have small to medium-sized nuclei, open chromatin, small or large nucleoli, and abundant cytoplasm [73]. Sarcomatoid squamous carcinoma is very rare variant, demonstrating areas of spindle-cell carcinomatous tumour confluent with poorly differentiated squamous cell carcinoma; immunohistochemistry demonstrates expression of cytokeratin and vimentin.



#### **23.4.4.1 Squamous Carcinoma In Situ**

Squamous carcinoma in situ is a precursor lesion of invasive squamous carcinoma. Squamous carcinoma in situ is characterized by full-thickness atypia of the cervical epithelium. Endocervical glands may also be involved. The epithelium is replaced by atypical cells that often have enlarged, oval nuclei, increased nuclear-to-cytoplasmic ratios, with mitotic figures.

#### **23.4.4.2 Microinvasive Carcinoma**

Microinvasive squamous carcinoma is associated with squamous intraepithelial neoplasia, and may arise from either the surface epithelium or from endocervical glands involved by dysplasia [74]. Microinvasive carcinoma often displays cells that are larger, with more abundant eosinophilic cytoplasm than cells in the adjacent dysplasia. A desmoplastic stromal reaction is usually present. These features are useful in distinguishing microinvasion from rounded, well-circumscribed endocervical glands involved by squamous dysplasia.

#### **23.4.4.3 Invasive Squamous Cell Carcinoma**

Invasive CC arises from high-grade dysplasia that may be detected up to 10 years before invasive carcinoma develops. Untreated squamous carcinoma in situ results in invasive carcinoma in about one-third of cases over a period of 10 years. Invasive carcinoma occurs most often after the age of 40 years, although it may be seen in young women. It is associated with HPV infection in more than 99% of cases. These tumours may consist of firm, indurated masses, or they may be ulcerated or polypoid.

Mitoses may be numerous, and atypical forms may be present. There is typically a desmoplastic stromal response around the nests of invasive neoplasm. Lymphatic and vascular space invasion may be present, especially in more deeply invasive tumors. Invasive squamous carcinomas are also graded [75], although treatment protocols do not depend on grade, and the histologic grade may not correlate with prognosis. Grade 1 (well-differentiated) tumors are not very common in the cervix. They display keratin pearls and large numbers of keratinized cells. Nuclei display only mild to moderate atypia, and mitoses are typically not numerous. Grade 2 (moderately differentiated) tumors represent the majority of invasive squamous carcinomas of the uterine cervix, and are usually nonkeratinizing squamous carcinomas with nuclear pleomorphism, numerous mitoses, and an infiltrative pattern. Grade 3 (poorly differentiated) tumors either have smaller cells without neuroendocrine differentiation, or are pleomorphic with anaplastic nuclei, and sometimes a tendency to form spindle cells that must be distinguished from sarcoma by positive cytokeratin stains.

### **23.4.5 Adenocarcinoma**

While the incidence of squamous carcinoma of the cervix has decreased in past decades owing to cytologic screening, the number of cases of cervical adenocarcinoma has increased [76, 77]. Adenocarcinoma of various types accounts for 20–25% of CCs [76].

About 80% of cervical adenocarcinomas are endocervical-type adenocarcinomas, which are composed predominantly of cells with eosinophilic cytoplasm, frequent apoptotic bodies, although many other patterns and cell types have also been observed.

### **23.4.6 Mucinous Adenocarcinoma**

There are several variants of mucinous adenocarcinoma of the cervix, including endocervical, intestinal, signet ring cell, minimal deviation, and villoglandular variants. HPV DNA has been detected in more than 90% of mucinous adenocarcinomas of the cervix, including endocervical, intestinal, and endometrial subtypes [78]. Endocervical-type adenocarcinomas are frequently referred to as mucinous; however, although some have abundant intracytoplasmic mucin, most have little or none [76].

### **23.4.7 Endometrioid Adenocarcinoma**

Endometrioid carcinomas of the uterine cervix are rare (about 7% of all cervical adenocarcinomas). These neoplasms display histologic features identical to endometrial carcinoma. Therefore, the possibility of a primary endometrial adenocarcinoma with endocervical extension or drop metastasis must be excluded before establish the diagnosis of primary endocervical endometrioid adenocarcinoma. Immunohistochemistry may help in difficult cases: combination of CEA positivity, ER and vimentin negativity is most often seen in endocervical primary tumours, while the reverse is more often characteristic of endometrial primary tumours. Evidence of association with HPV also supports an endocervical primary neoplasm [79].

### **23.4.8 Other Adenocarcinomas**

#### **23.4.8.1 Clear Cell Adenocarcinoma**

Clear cell carcinoma of the cervix has been associated with intrauterine diethylstilbestrol (DES) exposure; however, it also occurs in the absence of DES exposure. Patients usually have a cervical mass. The solid pattern of tumour displays sheets of

cells containing abundant glycogen-rich clear cytoplasm, atypical nuclei, and mitoses. The tubulocystic pattern contains tubules and cystic spaces lined by oxyphilic or clear cells. The papillary pattern is the least common variant and often coexists with solid or tubulocystic areas. Clear cell carcinomas of the cervix are not associated with HPV DNA [80].

#### **23.4.8.2 Serous Adenocarcinoma**

Papillary serous carcinoma of the uterine cervix has a bimodal age distribution, occurring in patients younger than 40 years and older than 65 years. This age distribution differs from the typical mid-life age of patients with cervical adenocarcinomas in general. Serous carcinomas of the cervix are not associated with HPV DNA [80].

Gross examination may reveal a nodular mass, an indurated cervix, or no visible abnormality. Microscopically, these tumours are identical to serous tumors of the ovary, endometrium, and primary peritoneal serous carcinomas. Considering the rarity with which this type of neoplasm is seen in the cervix, the diagnosis of primary serous carcinoma of the uterine cervix should be made only after excluding metastasis or extension of disease from another site, especially the endometrium [79].

### **23.4.9 Other Epithelial Tumours**

#### **23.4.9.1 Adenosquamous Carcinoma**

Adenosquamous carcinoma is a tumor composed of admixed malignant glandular and squamous elements. Adenosquamous carcinomas are more commonly associated with higher tumour grade ( $p < 0.001$ ) and vascular invasion ( $p = 0.002$ ) than are adenocarcinomas [81]. Adenosquamous carcinomas appear to be either histologically more aggressive or diagnosed at a later stage than adenocarcinomas of the uterine cervix.

#### **23.4.9.2 Glassy Cell Carcinoma**

Glassy cell carcinoma is a rare form of poorly differentiated adenosquamous carcinoma that displays cells with abundant eosinophilic cytoplasm, well-defined cell borders, ground-glass cytoplasm with large round to oval nuclei, prominent nucleoli, and a prominent infiltrate of eosinophils and plasma cells. Occasionally, this morphology may be seen in recurrences of adenocarcinomas or adenosquamous carcinomas that have been treated with radiation therapy [76].

### **23.4.9.3 Anaplastic Small Cell/Neuroendocrine Carcinoma**

Anaplastic small cell carcinomas resemble oat cell carcinomas of the lung and are made up of small tumour cells that have scanty cytoplasm, small round to oval nuclei, and high mitotic activity; they frequently display neuroendocrine features [68]. Anaplastic small cell carcinomas behave more aggressively than poorly differentiated small cell squamous carcinomas; most investigators report survival rates of less than 50% even for patients with early stage I disease, although recent studies of aggressive multimodality treatments have been somewhat more encouraging. Widespread haematogenous metastases are frequent, but brain metastases are rare unless preceded by pulmonary involvement [82].

### **23.4.10 Cervical Cancer Treatment**

When confronted with initial CC (IA1 – IIA) the most important clinical decision will be with which radical treatment to initiate by. Deciding whether to pursue surgery (Table 23.2) or radiotherapy (the latter typically combined with chemotherapy – cisplatin) is a controversy probably as old as the coexistence of these treatment options.

In a trial published in 1997, Landoni randomly allocated 337 patients to be submitted either to radiotherapy (without surgery) or to radical hysterectomy. No statistically significant difference was found in life expectancy between both groups [83]. However, insufficient data regarding these treatment options, especially after the advancements in both fields with the wide adoption of radio-chemotherapy and minimally invasive surgery, compromises direct comparisons. Therefore, the therapeutic strategy for uterine CC should be decided on an individual basis and determined by factors such as disease extension (estimated by the clinical stage, often established by FIGO – 2009), the patient's health status (age and comorbidities) and by specific considerations like the desire to preserve fertility.

### **23.4.11 Stage IA**

Stage IA involves microscopic lesions with horizontal or superficial extension and limited vertical invasion with low risk for lymphatic dissemination (less than 1%) [84]. Lesions classified as stage IA1 by the FIGO system and without angiolymphatic invasion are considered low risk lesions and eligible for a conservative surgical treatment [85]. The indicated surgical treatment in this scenario for women with no desire for future pregnancies is the extrafascial simple hysterectomy, which could be performed through the access that best suits the patient and surgeon's experience.

A wide cone biopsy (cold knife or LLETZ) could be performed in patients who desire fertility preservation as long as negative margins are obtained.

**Table 23.2** Rutledge et al. [86]

Rutledge, Piver & Smith89	Querleu & Morrow90	Procedure Description	Classic Indication
I	A	Extrafascial simple hysterectomy without important resection of parametria or vagina	Microinvasive cancer
II	B1	Radical hysterectomy where the uterine vessels are ligated at the crossing of the ureters as well as the section of the parametria; removal of the upper fourth of the vagina ( $\geq 1$ cm)	Microscopic tumor or macroscopic $\leq 2$ cm
N/A	B2	B1 + paracervical lymphadenectomy	
N/A	C1	Radical hysterectomy with section of the parametria at the level of the internal iliac vessels; removal of the upper third of the vagina ( $\geq 2$ cm); nerve sparing	Macroscopic tumor $> 2$ cm
III	C2	C1 but without nerve preservation "Wertheim-Meigs"	
N/A	D1	Radical hysterectomy with parametria resection extended laterally; resection and reconstruction of one or more internal iliac vessel	Recurrent disease invading the lateral pelvic wall (still undergoing investigation)
N/A	D2	D1 + resection and reconstruction of the pelvic wall – muscle and/or bone	
IV	N/A	Type III or C2 + extensive dissection of the ureter and section of the vesicouterine ligament adjacent to the bladder	Recurrent disease (rarely without prior treatment), with extension to the bladder (historical significance)
V	N/A	Type III or C2 + partial bladder resection and ureteral single or bilateral reimplantation	

Treatment for tumors stage IA2 remains controversial. According to literature, up to 13% of patients in this group may have positive lymph nodes. This relatively high incidence generally contributes to the indication of a more radical approach [88]. On the other hand, a recent literary review [89] suggests an incidence lower than 1% for lymph node positivity in stage IA2 patients. Historically, there has been a tendency to attribute an unfavourable prognosis to adenocarcinomas, contraindicating any attempt to a non-radical approach. However, recent case studies including one literary review [90], support that microinvasive cervical adenocarcinomas may be treated in the same manner as squamous cell carcinomas when in equivalent stages. The presence of angiolymphatic invasion in pathology reports, regardless of tumour histology or degree of invasion, considerably increases the risk for lymph node metastasis [91] and determines the necessity for a radical approach (refer to stages IB1 and IIA1 below).

### **23.4.12 Stages IB1 and IIA1**

Tumors up to 4 cm in diameter, limited to the cervix or compromising the upper third of the vagina, defines the patient population that most benefits from a radical surgical approach (radical hysterectomy combined with bilateral pelvic lymphadenectomy). Radical hysterectomy is not defined by a single technique but rather by a group of techniques united by a common denominator – removal of the uterus en bloc with the upper third of the vagina. The Rutledge, Piver and Smith classification [86] or even more recent, the Querleu and Morrow classification [87] define different classes of hysterectomies based on the extension of vaginal and parametrial resection with or without preservation of the hypogastric nerve plexus. The purpose of this discussion is not to provide a detailed description of each individual technique due to the variety and complexity of possible procedures and anatomical considerations. Table 23.2 summarizes the different classes of hysterectomies and each indication. Refer to the bibliographic references and surgical textbooks for further information. Note that none of the radical hysterectomy techniques described below include oophorectomy as a mandatory procedure. Given the rarity of occult metastatic involvement of the ovaries (<1%) in initial stages and the benefits of hormone function preservation in young women, ovarian-sparing hysterectomy could be a feasible option. The most frequently adopted procedures are the type II Piver radical hysterectomy (Querleu-Morrow B) and type III (Querleu-Morrow C-1 or C-2), the tumor size generally orienting the most indicated technique (2 cm cut-off). The most significant difference between these procedures, besides operative time, is hypogastric nerve plexus injury clinically manifested as bladder dysfunction, necessity for intermittent or permanent bladder catheterization, recurrent urinary tract infections and diminished quality of life. Less extensive procedures (type II or B) reduce manipulation of the hypogastric nerves, minimizing bladder function disruption. Furthermore, since the original prospective study [92], increasing evidence supports that type II or B radical hysterectomy could be sufficient treatment for lesions limited to the cervix up to 4 cm in diameter (refer to stages IB2 and IIA2 below). Recent studies have questioned the necessity for any degree of parametrial resection, suggesting the permanent substitution of the radical hysterectomy for the simple hysterectomy [87]. However, there is still no consensus that defines the ideal extent of resection, leading many centres to continue indicating type III or C hysterectomies. This practice increases the interest in nerve sparing surgery (type C1) intended to successfully combine surgical radicalness with decreased neurological morbidity [88].

### **23.4.13 Fertility Preservation**

The concept of fertility preservation originally described by Daniel Dargent in 1987 [89], consists of the resection of the cervix, proximal parametria and upper third of the vagina, conserving the uterine body which is anastomosed to the remaining

vaginal wall. This procedure, also known as radical vaginal trachelectomy, could be performed via abdominal incision or transvaginal as long as adequately complemented by pelvic lymphadenectomy, preferably through video laparoscopy. Subsequent studies [90] support that this feasible technique respects fundamental oncological principles present in traditional radical hysterectomy while successfully maintaining fertility, occasionally affected by cervical insufficiency or stenosis. The literature is limited regarding the use of this technique for gestation preservation in pregnant women [91]. The success rate for radical vaginal trachelectomy depends on adequate patient selection. Patients who require adjuvant radiotherapy (refer to adjuvant radiotherapy for indications) will experience endometrial and ovarian dysfunction, impairing the possibility for future pregnancies. As in Dargent's original series, current recommendation for this procedure is limited to patients with tumors up to 2 cm, yet a few studies have questioned this limit and even considered the possibility of neoadjuvant chemotherapy [92].

### **23.4.14 Minimally Invasive Surgery**

The amount of prospective and randomized evidence available comparing video laparoscopic versus conventional hysterectomy is still surprisingly scarce despite the existence of reports on laparoscopy dating back over 20 years [93] and the widespread practice of this procedure amongst the gynecologic oncology community [94]. Yet sufficient retrospective data [95] consistently support the advantages of a minimally invasive access such as blood loss reduction, faster reestablishment of intestinal function, less analgesics use and hospitalization period. Robotic video laparoscopic surgery is a recent technique apparently safe in experienced hands. Success rates are similar to those of conventional surgery [96] yet with improved practical conditions to perform nerve sparing surgery [97]. Other advantages include a smaller learning curve and inferior conversion rate when compared to regular video laparoscopy [98]. Its major limitation is the excessive financial cost, considerably reducing acceptance [99].

#### **23.4.14.1 Adjuvant Radiotherapy**

Patients submitted to radical hysterectomies presenting high risk factors for recurrence such as lymph node metastasis, stromal invasion over one third of the myometrial thickness, angiolymphatic invasion and tumor size greater than 4 cm, benefit from adjuvant radiotherapy due to increased locoregional control as seen in a major study [100]. Although with no statistical significance, a gain in survival rate was also observed after adjuvant radiotherapy although with increased morbidity, possibly as a result of the effects of radiation on a recently operated pelvis. Considering the similar results obtained through radical surgery or definitive radiotherapy [101] and the significant increase in morbidity after both treatment combination, there is

a tendency to interrupt surgery once positive lymph nodes are found and confirmed by intraoperative frozen section histopathology in order to reduce complication rates. Prospective studies [102] suggest that this is a safe practice and does not worsen the prognosis.

#### **23.4.14.2 Radiation Therapy**

Concurrent cisplatin-containing chemotherapy and radiation therapy is the treatment of choice for patients with locally advanced CC. The efficacy of concurrent chemoradiation over radiotherapy alone in the definitive treatment of locally advanced CC has been repeatedly demonstrated by prospective randomized trials. In a GOG/SWOG trial, 368 patients with stage IIB, III, and IV squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma were randomized and received either radiation therapy with concurrent hydroxyurea or concurrent radiation and chemotherapy (5-FU and cisplatin). The results showed that progression free survival (PFS) and overall survival (OS) were both statistically significantly improved in the group that received chemoradiation therapy ( $p = 0.033$ ) [103]. A similar GOG trial randomized 526 patients with stage IIB, III, or IVA cervical cancer without involvement of the paraaortic lymph nodes to (1) cisplatin 40 mg/m<sup>2</sup> weekly for 6 weeks; (2) cisplatin 50 mg/m<sup>2</sup> on days 1 and 29, followed by 5-FU 4 g/m<sup>2</sup> given as a 96-h infusion on days 1 and 29, and hydroxyurea 2 g/m<sup>2</sup> twice weekly for 6 weeks; or (3) oral hydroxyurea 3 g/m<sup>2</sup> twice weekly for 6 weeks. After a median follow-up of 3 years, the OS rate and relative risks of disease progression or death were significantly improved in the two groups receiving cisplatin based chemotherapy. However, there was no difference in the 2-year PFS, OS, local control, and lung metastases rates between the two chemotherapy arms [104]. A larger randomized multi-institution trial, RTOG 90–01, compared the effect of radiation therapy to the paraaortic lymph nodes and pelvis (45 Gy to both areas in 25 daily fractions) and concurrent chemotherapy and pelvic irradiation (45 Gy in 25 daily fractions). The results revealed that the addition of chemotherapy to pelvic radiation produced a significant improvement in 5-year disease-free survival (67% versus 40%), OS (73% versus 58%), and distant relapse (14% versus 33%) rates, as compared to patients treated with extended field radiation therapy only [105].

#### **23.4.14.3 Radiotherapy Techniques**

External irradiation is used to treat the whole pelvis, parametria and nodal areas, as the common iliac and paraaortic lymph nodes, whereas central disease (cervix, vagina, and medial parametria) is irradiated both with external beam with intracavitary sources.

Design of the external beam fields depends on the extent and volume of the tumor and takes into account the fact that cancer of the uterine cervix spreads in a very predictable manner, first spreading laterally to the para-cervical nodes, then to



the internal common iliac and finally to the paraaortic nodes. Approximately 15% of patients with FIGO stage I disease presents positive pelvic nodes, 30% of those with stage II and up to 45% of those with stage III. The risk of positive paraaortic nodes is roughly half that of the pelvic node rate (6% in stage I, 12% in stage II and 24% in stage III).

In the past, bony landmarks were often used to delineate the width of the pelvic field. On anteroposterior (AP) radiograph, the field edge used to be set at 1.5 and 2 cm of the widest point of the bony pelvis and it was thought that the pelvic nodes would easily be included. However, now with the advent of computed tomography (CT) simulations it is known that often these margins are not adequate and it is superior to perform a treatment planning CT with both intra venous and oral contrast agents. A prospective study showed that fields based solely on bony landmarks had at least one inadequate margin in 95.4% or an excess margin in 55.8% of patients [106].

CT-based planning is recommended and the target volume is the cervix, uterus, uterosacral ligaments and nodes deemed at risk or known to harbor metastatic disease. The uterus is easily seen by means of CT scan or MRI. Organs at risk (OAR) as bladder, rectum, small bowel, bone marrow and femoral heads should be outlined.

Guidelines strongly recommend MR imaging in target delineation due to the difficulty in distinguishing soft tissue components on CT. Either a diagnostic MR scan or an MR simulation scan, with the patient in the same treatment position, were recommended if resources allowed. Fusion of the T2-weighted axial MR images to the planning CT was recommended [107].

Tumor and enlarged nodes visualized on CT are outlined as gross tumor volume (GTV) and clinical tumor volume (CTV) should include the GTV, cervix (if not already encompassed by the GTV), uterus, parametria, ovaries, and vaginal tissues [107].

Usually a four field arrangement gives excellent dose distributions and allows for some sparing of small bowel and bladder and possibly some of the rectum. Care must be taken in designing the lateral fields so that the entire uterus is compassed and the utero-sacral ligaments, which attach at S1 and S2, are included. A common mistake is to try to block large portions of the rectum and, in doing so, shield the tumor extent posteriorly. Additionally, the uterus is often anteverted and a tight anterior margin can block some of the uterus. Additionally, in tumors involving the lower third of the vagina, the inguinal nodes are at risk and should be included in the external beam fields.

Appropriate measures must be taken to ensure that they receive adequate dose, such as using mixed energy beams and ensuring that the fields are wide enough to include them. The whole pelvic fields should be treated to 45–50.4 Gy with conventional fractionation (1.8 Gy or 2.0 Gy per fraction). The small bowel should be visualized by CT to ensure that the dose does not exceed 45 Gy.

Routine parametrial boost to treatment of parametrial extension based on FIGO staging is widespread [108], but CC with clinically involved parametria can be adequately treated without parametrial boost. Parametrial boosting leads to additional toxicity and underdosing of clinical target volume in patients with distorted anat-

omy without added benefit in outcome. So, if MRI and PET scans are available for staging, it is not necessary to use parametrial boosting [109].

Para-aortic irradiation is not recommended routinely if para-aortic adenopathy is absent. Concomitant boost to PET-positive pelvic lymph nodes can reduce the incidence of lymph node recurrence, as reported by Vargo et al. [110], that found 4.9% regional node failure in 61 CC patients (stage IB1–IVA) with PET-avid pelvic lymph nodes treated with extended-field IMRT 45 Gy in 25 fractions and a concomitant boost to a median of 55 Gy for positive lymph nodes. Median total equieffective dose (EQD2) of 62.6 Gy to bulky lymphadenopathies of CC patients through tomotherapy can result in complete response and this lymph node response was a significant prognostic factor for OS ( $p = 0.016$ ) [111].

In the era of image-guided adaptive radiotherapy, accurately defining disease areas is critical to avoid irradiating normal tissue. Based on additional information provided by FDG-PET, radiation treatment volumes can be modified and higher doses to FDG-positive lymph nodes safely delivered. FDG-PET/CT has been used for image-guided brachytherapy of FDG-avid tumor volume, while respecting low doses to bladder and rectum [112].

#### **23.4.14.4 IMRT Rapid Arc**

The use of intensity-modulated radiotherapy (IMRT), in static beams [113, 114] and volume-modulated arc therapy (VMAT) allows a comparable or better dose distribution to the clinical target volume with decrease of toxicity as it reduces the dose to bladder, rectum, bowel and bone marrow.

The use of IMRT significantly reduces acute gastrointestinal toxicities, in comparison with the available data for conventional radiotherapy [115].

VMAT advantages over IMRT are better homogeneity of the planning target volume coverage, while decreasing the treatment time [116] (Figs. 23.1 and 23.2).

There were some concerns regarding IMRT and CC irradiation considering internal organ motion and tumor regression. Image-guided radiation therapy (IGRT) may reduce the probability of a geographic miss during treatment delivery for cervical cancer patients, allowing adjustment and correction of the radiation beam or the patient's position, and thus a more accurate form of dose delivery for patients [117].

#### **23.4.14.5 Brachytherapy**

Radiation therapy for CC consists of a combination of external whole pelvic irradiation and intracavitary irradiation. Brachytherapy is the insertion of radioactive sources in contact with the tumor. In this way, the treatment is delivered from the 'inside out', conferring some advantages as dose delivery and its heterogeneity, doses variations called gradient, occurring within the tumor volume.

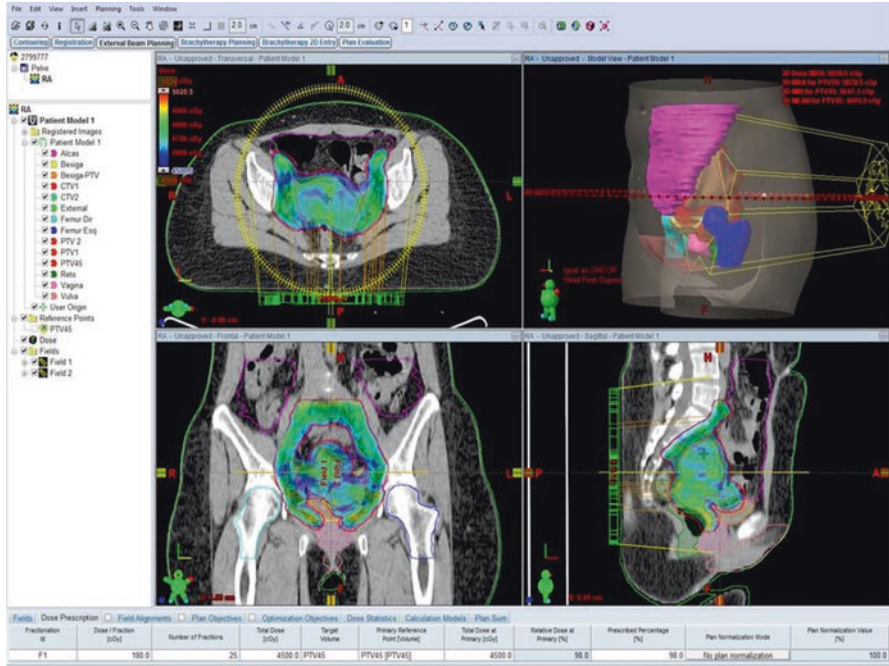


Fig. 23.1 IMRT Rapid Arc

Brachytherapy is an important component of the treatment for locally advanced CC. Radiation therapy associated with brachytherapy leads to higher pelvic control rates than exclusive radiation therapy (67% vs. 45%) and greater survival in 4 years (46% vs. 19%) [118].

Shorter time to completion of radiation therapy is associated with longer survival in women with CC and should be a goal in treatment. Overall radiotherapy treatment time should be within 55 days. Data in a large observational cohort suggest that should be within 64 days, with limited survival benefit at 10 weeks [119].

EBRT is given initially to decrease the bulk of the tumor, providing a better geometric anatomy and allowing optimal dose delivery in intracavitary brachytherapy (ICBT). Brachytherapy can be initiated prior the completion of external beam radiation to the pelvis. In locally advanced tumors, the majority of the external beam therapy is given prior initiating brachytherapy in order to shrink the tumor. The greatest decrease in tumor volume occurs during EBRT, of the order of 75% reduction, usually after 3 weeks of treatment, whereas regression throughout the time period of the brachytherapy fractions is minor, only some 10% [120].

High dose rate (HDR) and low dose rate (LDR) are both effective in the treatment of CC and the effects are equivalent in prospective randomized trials, with no difference in 5-year local control or OS for stage I-III CC [121].

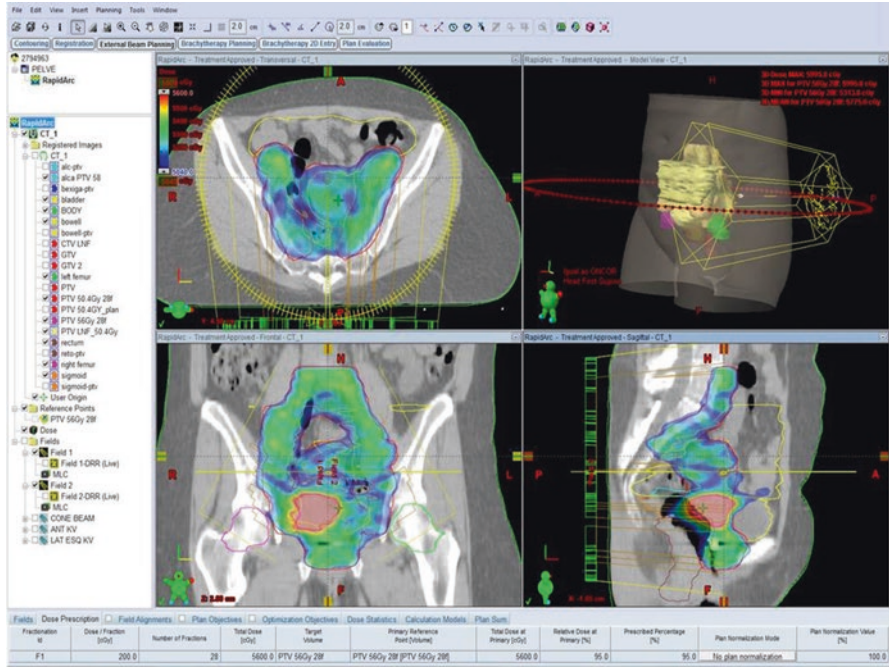


Fig. 23.2 IMRT Rapid Arc

Treatment is delivered under anesthesia, using tandem and vaginal ovoids or ring. Patients with persistent vaginal disease, tandem and cylinder can be considered. For more advanced disease, an interstitial implant might be indicated, if persistent disease is observed, including sidewall disease or vaginal disease thicker than 5 mm.

Radiation dose correlates with local control. External-beam radiation therapy is followed by or mixed with different schedules of ICBT, as 3 fractions of 8.5 Gy [122], 4 fractions of 7 Gy each, 5 fractions of 6 Gy, 6 fractions of 5 Gy, 5 fractions of 5.5 Gy [123]. Routine use of equivalent dose in 2 Gy fractions (EQD2) is recommended for gynecologic brachytherapy as it is reproducible and able to compare different dose rate and dose fractionation schedules [124]. Values for  $\alpha/\beta = 10$  Gy for cervical tumor  $\alpha/\beta = 3$  Gy for OAR (bladder, rectum, sigmoid) are commonly used.

Findings from a multicenter, international clinical trial for locally advanced CC showed significantly better tumor control following four fractions of 7 Gy each than following two fractions, 9 Gy each, of high-dose-rate (HDR) brachytherapy, but neither OS nor severe treatment-related side effects differed between the treatment groups [125].

The recommended tumor dose in 2 Gray (Gy) per fraction radiobiological equivalent (EQD2) is 80–90 Gy, depending on tumor size at the time of brachytherapy

[123]. Image-guided adaptive brachytherapy for CC, applying high radiation doses of 85 Gy EQD2 (“equivalent dose in 2 Gy fractions”), reaches 90% local control at 3 years in stage I/II and about 85% in stage III/IV. Further increase in the dose to point A beyond 85Gy was not associated with improved central control, but rather correlated with additional complications [126].

According to International Commission on Radiation Units and Measurements (ICRU) [124] Report No. 81 minimum standard for reporting is Point A dose, bladder and recto-vaginal point dose. Point A is defined in relation to the applicator of brachytherapy [127]. Advanced standard for reporting includes also estimated dose in the CTV and vaginal point doses down at level of sources.

Introduction of image guided brachytherapy (IGBT) for CC has led to significantly increased 3-year locoregional control and survival rates, whilst reducing late morbidity [128].

Potter [129] clearly confirm that excellent local control rates can be achieved through MRI guided adaptive brachytherapy following a protocol according to the concepts of the GEC ESTRO recommendations, with an overall local control rate of 95% at 3 years including 103/156 (66%) patients with tumour size >5 cm. This translates into an absolute local control benefit of 23–26% (actuarial) and a relative reduction in local failure of about 65% compared to the historical Vienna series.

Stereotactic body radiotherapy can achieve good dose coverage of the target volumes with low toxicity and favorable early tumor control in patients who could not undergo brachytherapy [130].

A recent Surveillance, Epidemiology, and End Results study with over 7000 patients highlighted the importance of brachytherapy in CC management. Brachytherapy resulted in higher cancer specific survival rates (64 vs. 52%), and 4-year OS (58 vs. 46%). Unfortunately, this study also reported a decreased utilization rate of brachytherapy with increase of IMRT or SBRT boost. It resulted in inferior OS as compared with brachytherapy [131].

#### **23.4.14.6 Radiation Side Effects and Complications**

Commonly observed acute radiation-induced complications include enteritis (diarrhea and/or abdominal cramping), proctitis (anorectal discomfort, tenesmus, or rectal bleeding), and cystourethritis (frequency, dysuria, and/or nocturia). Most of these symptoms can be medically treated.

Late complications observed include vaginal stenosis that can be prevented and treated with a vaginal dilator. Vaginal ulceration or necrosis occurs in approximately 7% of patients typically at 6–12 months after treatment. Supportive measures are recommended, and the symptoms usually subside in 1–6 months. Late gastrointestinal complications can occur for up to 19 months, and late genitourinary complications can occur for up to 2 years.

### 23.4.15 *Treatment of Locally Advanced Disease*

Patients with locally advanced disease (stages IIB, III and IVA) comprise a significant proportion of the total population with CC, particularly in developing countries. Women with locally advanced disease have a higher rate of recurrence and worse survival than those with early stage disease. With radical surgery or definitive radiotherapy, treatment results are unsatisfactory. After surgery alone, the rate of relapse is at least 30%, and 5-year survival rates range from 80% for stage IB disease to 30% for stage III disease [132]. With radiotherapy alone, the 5-year survival rate has historically been 60–65%, and the pelvic failure rate 18–40% [133]. With these treatment modalities, the patterns of failure are characterized by both local and distant metastases. However, the main cause of failure is uncontrolled disease within the pelvis [134].

The utility of cytotoxic chemotherapy in this clinical context has been the subject of extensive clinical investigations, with variable results. Regarding neoadjuvant chemotherapy, its use prior to definitive hysterectomy as an alternative to primary chemoradiation has not been studied. While two meta-analyses suggested a benefit to neoadjuvant chemotherapy plus surgery for women with locally advanced CC, the comparisons were to single modality treatment with primary surgery or radiation therapy, which are no longer considered appropriate treatment options [135]. As ineffective chemotherapy may prejudice response to radiation simply by delaying its initiation, until regimens are developed that produce a high response rate, neoadjuvant chemotherapy is potentially risky. Two ongoing phase III trials will help to clarify the impact of neoadjuvant chemotherapy versus concomitant chemoradiation in women with advanced disease (EORTC 55994 and a study sponsored by the Department of Atomic Energy of India. Using chemotherapy as a radiation sensitizer is an attractive approach, as it may increase tumour control, without delaying the beginning of radiotherapy. In 1999, a series of five randomized trials conducted in the United States in the mid and late 1990s, became mature [103–105, 136]. The trials involved a total of 1894 women in which radiotherapy would be used. Collectively, all five trials comparing cisplatin-based chemoradiation to radiation alone in locally advanced CC patients showed a significant reduction in the risk of recurrence and death with cisplatin-based chemoradiation. Following these five trials, a sixth large randomized trial comparing cisplatin-based chemotherapy to radiation therapy alone for locally advanced CC was reported from the NCI Canada [137] and a statistical benefit was not seen in the chemoradiation arm. Despite these conflicting results, the pooled analysis of all six trials demonstrated a survival benefit with improved local control in the chemotherapy-treated patients. And this benefit was further confirmed in a 2010 meta-analysis [138]. According to the meta-analysis, patients who received chemotherapy presented a reduction in the risk of death (HR 0.69, 95% CI 0.61–0.77), which translated into a 10% absolute improvement in survival; a reduction in the risk of recurrence (HR 0.66, 95% CI 0.59–0.73), which translated into a 13% absolute improvement in progression-free survival; a reduction in the risk of local recurrence (OR 0.59, 95% CI 0.50–0.69);

and a trend towards a reduction in distant metastases (OR 0.81, 95% CI 0.65–1.01). The survival benefit associated with chemoradiation significantly decreases with increasing stage. For women with stage IB to IIA, IIB, and III to IVA CC, the 5-year survival benefit was 10, 7, and 3%, respectively ( $p = 0.017$ ).

Concurrent cisplatin-containing chemotherapy and radiation therapy is the treatment of choice for patients with locally advanced CC. The use of cisplatin 40 mg/m<sup>2</sup> weekly for 5 or 6 weeks is an acceptable option, easy to perform and with low toxicity rate.

Recently, a trial included 424 women with stage IIIB squamous cell carcinoma of the uterine cervix to receive cisplatin plus radiation therapy versus radiation therapy alone. At a median follow-up of 88 months the 5-year DFS was significantly higher in the combination arm (52.3%; 95% CI, 52.2%–52.4%) compared with the radiation therapy arm (43.8%; 95% CI, 43.7%–43.9%), with a hazard ratio for relapse or death of 0.81 (95% CI, 0.68–0.98) ( $p = 0.03$ ) and the 5-year (OS) was significantly higher in the combination arm (54.0%; 95% CI, 53.9%–54.1%) compared with the radiation therapy arm (46.0%; 95% CI, 45.9%–46.1%), with a hazard ratio for death of 0.82 (95% CI, 0.68–0.98;  $p = 0.04$ ), providing high evidence in favor of concurrent weekly cisplatin chemotherapy in this setting.

Cisplatin plus gemcitabine is one of the doublets that are active and well tolerated for disseminated disease [139]. Exploring the synergistic activity of cisplatin, gemcitabine and radiotherapy, Dueñas-Gonzales et al. [140] reported the results of an important phase III study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA CC. The addition of gemcitabine seems to improve survival outcomes in women with locally advanced CC. Moreover, distant failure rate, which contributes to most of failures and mortality in CC, was significantly lower in the gemcitabine arm. However, the comparison of the proposed experimental regimen with the standard treatment for locally advanced disease provided more grade 3 and 4 toxicities, treatment discontinuations, hospitalizations and deaths. As it is not clear whether the benefits of the investigational treatment were due to the use of cisplatin plus gemcitabine during RT or following chemoradiation, most groups continue to prescribe cisplatin alone during chemoradiation.

Focusing on adjuvant chemotherapy, there is limited evidence of benefit to justify administering systemic chemotherapy after chemoradiation. However, some data suggest that there is a role for it. In the trial conducted by Dueñas-Gonzales, women who received two cycles of systemic intravenous cisplatin plus gemcitabine after chemoradiation had significant improvements in both PFS and OS compared with women who received cisplatin alone-based chemoradiation. Given the concerns for toxicity and the unclear contribution of systemic treatment in this study, further results are awaited. Adding chemotherapy, carboplatin and paclitaxel, after chemoradiation is currently being addressed by the Outback trial, which is a randomised phase III trial for women with locally advanced cervical cancer (stage IB1 and node positive, IB2, II, IIIB or IVA). Women are randomized to standard cisplatin-based chemo-radiation or standard cisplatin-based chemo-radiation followed by 4 cycles

of carboplatin and paclitaxel chemotherapy. The primary objective is to determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemo-radiation improves OS [141].

In summary, cure rates of locally advanced CC have reached a plateau. Current therapy results are sub-optimal and patients with stage III and IVA tumours have 5-year survival rates of 40% and 15%, respectively [63]. These circumstances highlight the limitations of traditional therapy and the need to explore new strategies to improve prognosis in this group of patients.

### **23.4.16 Metastatic Disease**

Most patients with CC present with locally advanced disease (i.e., IIB, III, and IVA), and the majority of them relapse, especially in stages III and IVA [142]. Patients who present with disease in distant organs are almost always incurable. The care of these patients must emphasize palliation of symptoms with use of appropriate pain medications and localized radiotherapy. Tumors may respond to chemotherapy, but responses are usually brief [63]. Patients with advanced or recurrent CC have poor prognosis (1-year OS around 20%) and generally, those women are managed with palliative chemotherapy aiming symptoms control, quality of life, and, when feasible, prolongation of life.

Metastatic and recurrent CC may present as nodal disease involving the para-aortic and/or supraclavicular nodes, limited disease involving one organ site, or widely metastatic disease. Locally recurrent CC usually presents with vaginal symptoms (i.e., discharge, bleeding, dyspareunia, or pain). On pelvic exam, a mass or nodularity at the vaginal cuff, which may extend to the side wall, may be visualized. Disease within the vaginal vault can be tender to palpation and prone to bleeding. Patients presenting with isolated metastatic findings on imaging should undergo a biopsy to prove metastatic disease, as there is a risk that these findings may represent a second primary malignancy or a benign process [143].

Patients with metastatic CC can present with no symptoms or non-specific complaints (i.e., fatigue, nausea, or weight loss). Women who present with signs (ie, weight loss, palpable abdominal lesions, leg oedema) or symptoms should undergo radiologic imaging to evaluate for metastatic disease.

The most commonly used imaging modalities include CT and PET with or without CT. PET-CT has a sensitivity of 93–96% and specificity of 93–95% [144]. In addition, the results from a PET-CT scan often lead to changes to the therapeutic plan for women with recurrent disease by sparing women from an extensive surgical approach in the setting of widely metastatic disease [145].

For women who present with a local relapse, treatment directed to the site of recurrence can be performed with curative intent. Options include hysterectomy, pelvic exenteration (most often an anterior exenteration) [80] or radiation therapy; the choice depends on the patient's prior treatment. Commonly employed criteria to identify those women most likely to benefit from surgery include [146]: a central



pelvic recurrence without side wall fixation or associated hydronephrosis, a long disease-free interval and tumour size of the recurrence less than 3 cm in diameter. If total pelvic exenteration will be performed, it must involve a detailed medical and imaging evaluation as well as careful counselling of the patient and family regarding the extent of surgery and postoperative expectations. The surgical mortality rate is less than 10%. The 5-year survival rate for patients who undergo anterior pelvic exenteration is 33–60%; the 5-year survival rate for those who undergo total pelvic exenteration is 20–46% [147].

For women who underwent primary radiation therapy, radical hysterectomy for management of local recurrence is an approach associated with 5-year survival rates ranging between 30% and 40% [148, 149]. However, surgical complications are more common in this setting. In one study, 15 of 34 patients who underwent surgery for persistent or recurrent disease following radiation therapy, experienced major postoperative complications, including fistula formation.

The treatment of choice for patients who have an isolated pelvic recurrence after initial treatment with radical hysterectomy alone is aggressive radiotherapy [80]. Pelvic wall recurrences are often treated with external-beam irradiation alone, although surgery and intraoperative radiotherapy may contribute to local control in selected patients [149]. Patients with vaginal recurrence usually have a better prognosis than those with pelvic wall recurrence. It is reported lower rates of successful salvage therapy for patients with locally recurrent adenocarcinoma [150].

For women who have undergone hysterectomy (with or without adjuvant radiotherapy or chemoradiation), pelvic exenteration represents the only potentially curative option for local recurrence or persistent disease. Careful patient selection is required given the perioperative and postoperative morbidity associated with this extensive surgical approach.

Radiation therapy is a reasonable option for patients who have not previously received it or women with operable disease who do not opt to proceed with pelvic exenteration. The benefit of radiotherapy was demonstrated in a single institution experience of 35 women who were treated with high-dose radiotherapy following a pelvic recurrence [151]. The 5- and 10-year survival rate was 43 and 33%, respectively, and pelvic control rates were 69 and 62%, respectively. The use of brachytherapy and a long treatment-free interval between primary surgery and diagnosis of recurrence were positive predictors of a good outcome. Given the superiority of concomitant chemotherapy with radiation therapy (chemoradiation) over radiation therapy alone as primary treatment, most experts prefer chemoradiation for these patients. Patients who have previously been treated with radiation therapy and those who are not candidates for surgical resection should be offered chemotherapy. The approach to these patients is identical to the treatment of women with metastatic disease. Chemotherapy has activity for the treatment of CC, although treatment is less successful if the recurrence is in an area that was previously irradiated.

The management of metastatic CC depends on the extent of disease at presentation. Women who have metastatic disease limited to the nodes the prognosis is poor. In a retrospective study of 375 patients with recurrent CC, the rate of OS at 5 years

was 27 and 0% for women with limited metastatic disease involving the paraaortic nodes ( $n = 60$ ) or the supraclavicular nodes ( $n = 26$ ) [152]. There are limited data to help guide treatment of women with metastatic disease limited to the lymph nodes. Some experts prefer systemic chemotherapy, while others prefer radiation therapy (with or without chemotherapy). A choice between them depends on institutional practice and patient preference. Chemotherapy-naïve patients have a higher response rate than women who received prior chemotherapy, including as part of chemoradiation [153, 154]. In the palliative scenario, cisplatin is widely studied and is the most active single agent [63, 155], with response rates (RRs) of 18–50% with doses ranging from 50 to 100 mg/m<sup>2</sup> intravenously every 3 weeks, compared with an RR of 28% in a phase II study using carboplatin and around 11–22% with irinotecan, ifosfamide, paclitaxel, vinorelbine, topotecan, or bevacizumab used as monotherapy [139, 156]. The clinical utility of these drugs in patients who have not responded to cisplatin or who have experienced recurrence or progression after chemoradiation is uncertain [63]. It is well recognized that the objective rate of response to chemotherapy is lower in previously irradiated areas (e.g., pelvis) than in non-irradiated sites (e.g. lung) [157].

There are several agents with activity in CC, which can be used as part of a combination regimen or as single agent therapy. The results of two phase 3 randomized trials, published in 2004 and 2005, have provided the first solid evidence that combination chemotherapy can improve both PFS (cisplatin plus paclitaxel vs single-agent cisplatin [158], cisplatin plus topotecan vs single-agent cisplatin [159]) and OS (cisplatin plus topotecan vs single-agent cisplatin [159]) when it is administered for recurrent or metastatic CC.

The comparison between cisplatin as single agent with the combination of paclitaxel plus cisplatin (T + P) in patients with squamous cell CC in GOG (Gynecologic Oncology Group) 169 study has resulted in a higher RR (19% vs 36%,  $P = 0.002$ ) and longer median PFS (2.8 vs 4.8 months) with no significant difference in quality-of-life scores; however, median OS was similar in both arms [158]. The first phase III trial that demonstrated a survival advantage for combination chemotherapy over cisplatin alone in first palliative line has compared cisplatin to its combination with topotecan in GOG 179. Patients receiving cisplatin plus topotecan had statistically superior outcomes to those receiving cisplatin alone, with a median OS of 9.4 versus 6.5 months ( $P = 0.017$ ), a median PFS of 4.6 versus 2.9 months ( $P = 0.014$ ), and RR of 27% versus 13%, respectively. Indeed, a significant increase in the toxicity was presented (1% of grades 3 and 4 neutropenia with cisplatin monotherapy against 70% with combined therapy) [159]. A phase III trial, GOG 204, was performed to define the best cisplatin doublet among women with advanced or relapsed CC, including patients with squamous, adenocarcinoma, or adenosquamous cell carcinoma. Four doublets, the reference arm T + P and the three comparator arms cisplatin plus vinorelbine, cisplatin plus gemcitabine, and cisplatin plus topotecan, were evaluated. This study was discontinued in the planned interim analysis for futility. None of the tested regimens was superior; nevertheless, the trend in RR, PFS, and OS has favoured T + P [139]. For cisplatin plus paclitaxel, the overall response rate (ORR) was 29%. The ORR was 26, 22, and 23%, for cisplatin administered with

vinorelbine, gemcitabine, or topotecan, respectively. There was no difference in the risk of death among any of the experimental regimens compared to cisplatin plus paclitaxel.

Interestingly, the GOG 179 study reported higher RRs in patients not previously treated with platinum therapy (20% vs 8% in the cisplatin arm and 39% vs 15% in the cisplatin-topotecan arm). It suggests that recurrent CC following concurrent chemoradiation is more likely to be platinum-resistant. Adequate drug distribution may be limited for recurrences in previously irradiated tissues because of secondary fibrosis and compromised blood supply related to microvascular disruption. Concomitant chemoradiation is the standard of care in early CC; therefore, this issue requires careful attention regarding emerging palliative treatments in this patient group.

In the GOG 204 [139], former chemoradiotherapy is associated with an increased risk of death, and platinum-free-interval (PFI) has been reported as a prognostic factor for second platinum therapy [160]. Therefore, in advanced and persistent/recurrent CC not amenable to curative therapy, the combination of T + P is a worldwide current first choice for systemic treatment. However, a recently reported phase 3 trial comparing combinations of cisplatin with either topotecan, paclitaxel, gemcitabine, or vinorelbine revealed no significant differences in outcome between patients treated with the four cisplatin-based regimens [139].

Nowadays, women with recurrent, metastatic, or advanced CC should receive treatment consisting of a platinum-based combination plus the angiogenesis inhibitor bevacizumab as first line setting. Treatment incorporating bevacizumab was shown to improve OS in these patients. However, the costs of therapy may require scrutiny in comparison to the benefits and risks of incorporating bevacizumab in this setting, especially in underdeveloped areas. This recommendation is based on the results of GOG 240, in which 452 women were randomly assigned to chemotherapy with or without bevacizumab. Previous platinum-based therapy was administered with RT in 75 and 74% of patients, respectively. As presented at the 2013 American Society of Clinical Oncology meeting, chemotherapy plus bevacizumab resulted in an improved OS compared to chemotherapy alone (median, 17 versus 13 months, respectively; HR 0.71, 95% CI 0.54–0.94), PFS (median 8 versus 6 months; HR 0.67, 95% CI 0.54–0.82) and ORR (48 versus 36%) [161]. The final data published in 2017 showed that treatment with bevacizumab was also associated with higher toxicity, such as serious (grade 3/4) bleeding (5 versus 1%), venous thromboembolic disease (9 versus 2%), and gastrointestinal fistula (3 versus 0%). However, there was no difference between the study arms in quality of life up to 9 months following the therapy. The combination of bevacizumab and chemotherapy resulted in longer OS (16.8 versus 13.3 months) and PFS (8.2 versus 6.0 months) than chemotherapy alone [162]. Taken together, these results support the use of chemotherapy plus bevacizumab as a first-line treatment of metastatic CC.

Regardless of whether bevacizumab is also administered in the first-line setting, it is suggested a platinum-based combination. Because of the toxicity seen with cisplatin-based combination chemotherapy, carboplatin is a reasonable substitute for cisplatin, particularly for patients with medical comorbidities (e g, pre-existing

renal failure) and those patients previously treated with cisplatin-based chemoradiation. Carboplatin is less toxic than cisplatin in terms of nephrotoxicity, neurotoxicity, and emetogenicity. Data from a randomized phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent CC performed by the Japan Clinical Oncology Group (JCOG0505 study) showed that the carboplatin doublet was non-inferior to the cisplatin doublet in terms of OS [163]. In this study, 253 women with stage IVB, persistent or recurrent CC were randomly assigned for treatment with cisplatin (50 mg/m<sup>2</sup>) plus paclitaxel (135 mg/m<sup>2</sup>) or carboplatin (area under curve [AUC] 5) plus paclitaxel (175 mg/m<sup>2</sup>), administered every 3 weeks for six cycles. Prior cisplatin therapy (primarily with chemoradiation) was noted in 43 and 50% of each group, respectively. Compared to cisplatin plus paclitaxel, treatment with carboplatin and paclitaxel resulted in similar ORR (63 versus 60%), no difference in OS (HR for mortality 0.99, 90% CI, 0.79–1.25) and significantly less serious (grade 4) neutropenic events (45 versus 75%,  $p < 0.0001$ ). There were also less serious (grade 3/4) incidences of renal insufficiency (0 versus 2.4%), nausea, and vomiting (3 versus 7%). However, carboplatin plus paclitaxel resulted in more neuropathic events (7 versus 1%). The results of JCOG0505 establish carboplatin and paclitaxel as a reasonable alternative to cisplatin plus paclitaxel in the treatment of women with metastatic CC, particularly in those who are not candidates for cisplatin and/or were previously treated with cisplatin-based chemoradiation.

### 23.5 Second-Line Therapy

For women who have progressed after first-line treatment and those patients who are not candidates for combination chemotherapy, it is suggested single agent chemotherapy. However, there is no evidence that treatment in the second or later line setting improves overall survival compared to best supportive care in this population.

Anti-programed cell death-1 (PD-1) immune checkpoint inhibitors have been evaluated in this setting. Pembrolizumab was assessed in a prospective phase Ib study in women with PD-L1-positive tumor cells and disease progression after first-line therapy for metastatic or recurrent CC. The results of this study showed that the ORR was 17% (4/24 patients) and median duration of response was 5.4 months. This was a small study (KEYNOTE-028), and the use of pembrolizumab for this indication is still investigational [164].

A choice among active agents must be tailored to the individual patient, with consideration to prior therapies received, residual toxicity, and performance status. Given the limited activity of currently available agents, it is encouraged participation in clinical trials exploring alternative approaches to metastatic CC.

Some active single agents are:

- Carboplatin – ORR 15% [165]
- Nanoparticle albumin-bound paclitaxel (125 mg/m<sup>2</sup> on days 1, 8, and 15 every 28 days) – ORR 29% [166]
- Vinorelbine (30 mg/m<sup>2</sup> IV push weekly for 2 weeks every 21 days) – ORR 15% [167]
- Paclitaxel (175 mg/m<sup>2</sup> IV every 3 weeks with dose reduction to 135 mg/m<sup>2</sup> if patients received prior RT) – ORR 20–25% [168]
- Pemetrexed (900 mg/m<sup>2</sup> IV every 3 weeks) – ORR 15% [169]
- Ifosfamide (1.2 g/m<sup>2</sup> IV daily for 5 days every 28 days) – ORR 22% [170]
- Topotecan (1.5 mg/m<sup>2</sup> IV daily for 5 days every 21 days) – ORR 19% [171]
- Irinotecan (125 mg/m<sup>2</sup> IV every 3 weeks) – ORR 15% [156].

### 23.5.1 *Molecular Target Agents*

Several recently reported studies have addressed the role of molecular targeted agents in recurrent or metastatic CC. In a phase II trial conducted by the GOG, bevacizumab was well tolerated and active in the second and third line treatment of patients with recurrent CC [172].

Pazopanib, another antiangiogenic agent that targets vascular endothelial growth factor receptor and platelet derived growth factor receptor, was shown to be well tolerated and demonstrated activity in recurrent or metastatic CC [173].

On the contrary, agents that target the epidermal growth factor (EGFR) and/or the human epidermal growth factor receptor 2 (HER2/neu) such as cetuximab or lapatinib have demonstrated limited activity in recurrent or metastatic CC [173, 174]. Cetuximab is well tolerated but has only modest activity in this population, which may be limited only to patients with squamous cell histology [174].

### 23.5.2 *Vaccines*

As the knowledge of the role of HPV infection in the natural history of preinvasive and invasive lesions of the lower genital tract was improved, prophylactic vaccination has emerged as an important element in CC prevention [79]. The aim of prophylactic vaccination is to generate neutralizing antibodies against the HPV L1 and L2 capsid proteins. Prophylactic vaccine development against HPV has focused on the ability of the L1 and L2 virion structural proteins to assemble into virus like particles (VLPs). VLPs mimic the natural structure of the virion and generate a potent immune response [63]. VLPs primarily induce a humoral response with

neutralizing antibodies, but they also induce cell-mediated immune responses [79]. Because the VLPs are devoid of DNA, they are not infectious or harmful. HPV VLPs can be generated by expressing the HPV capsid protein L1 in baculovirus or yeast [63]. VLP are combined with different aluminum based adjuvants, which stimulate the immune system and increase the response to vaccination.

It is estimated that if women were vaccinated against all high-risk types of HPV before they become sexually active, there should be a reduction of at least 85% in the risk of CC, and a decline of 44–70% in the frequency of abnormal Papanicolaou (Pap) smears attributable to HPV [5]. Based on the natural history of HPV infection and development of preinvasive and invasive disease, it may take at least 15 years before there is a significant impact on the incidence of CIN 2/3 and perhaps 30 years before there is a change in CC incidence [79]. Therefore, therapeutic vaccines are still very much needed to reduce the morbidity and mortality associated with CC.

The therapeutic approach to patients with preinvasive and invasive CC is to develop vaccine strategies that induce specific CD8+ cytotoxic T lymphocyte (CTL) responses aimed at eliminating virus-infected or transformed cells. The majority of CC express the HPV-16-derived E6 and E7 oncoproteins, which are thus attractive targets for T-cell-mediated immunotherapy.

Two vaccines are approved in the United States for the prevention of CC. The quadrivalent vaccine Gardasil (Merck & Co., Inc., Whitehouse Station, NJ, USA) contains VLPs to HPV types 6, 11, 16, and 18 and the bivalent vaccine Cervarix (Glaxo Smith Kline, Rixenstart, Belgium) contains VLPs to HPV types 16 and 18 [79].

Adequate antibody responses have been reported following immunization with quadrivalent and bivalent vaccines [175]. Efficacy studies were restricted to sexually active females, 15 years of age and older. There is no defined minimum threshold titer for protection. Seroconversion from prior exposure has been shown to reduce the risk of incident HPV infection, suggesting that the titers resulting from natural infection, which are lower than those elicited in vaccine studies, provide some level of protection [79, 176].

Quadrivalent HPV vaccine (Gardasil) – Results of two large randomized clinical trials in more than 17,000 adolescents and young females [177, 178] show that among HPV-naïve populations, the efficacy for preventing CIN2 or more severe disease due to HPV types included in the vaccine, was 97–100%. Data collected outside the clinical trial setting are also favorable, demonstrating decreased prevalence of HPV-related cervical disease and genital warts following introduction of quadrivalent vaccine into national immunization programs.

Gardasil is widely available and has been approved in many countries throughout the world for the prevention of cervical, vulvar, and vaginal cancers and their precursor lesions (i.e., cervical, vulvar, and vaginal intraepithelial neoplasia) caused by HPV types 6, 11, 16, and 18 as well as genital warts caused by HPV 6 and 11.

Bivalent HPV vaccine (Cervarix) – A large randomized clinical trial with more than 18,000 young females aged 15–25 years found that [179] among HPV-naïve patients, the efficacy of the bivalent vaccine for preventing CIN2 or more severe disease due to HPV types included in the vaccine was 93%, comparable with the

efficacy of the HPV quadrivalent vaccine. All results are consistent with those seen with HPV quadrivalent vaccine. The bivalent HPV vaccine (Cervarix) is widely available and has been approved in many countries throughout the world. This vaccine was also effective against other lesions caused by HPV types 31, 33, and 45, which are closely related to HPV 16 and 18 [79].

### **23.5.3 Recommendations for HPV Immunization**

#### **23.5.3.1 Timing of Immunization**

Clinical trial data of vaccine efficacy in males and females suggest that immunization with HPV vaccine is most effective among individuals who have not been infected with HPV, which is also more cost-effective. Thus, the optimal time for HPV immunization is prior to an individual's sexual debut. Neither vaccine treats [79] or accelerates the clearance of preexisting vaccine-type HPV infections or related disease.

Females who are sexually active should still be vaccinated consistent with age-specific recommendations. A history of an abnormal Papanicolaou test, genital warts, or HPV infection is not a contraindication to HPV immunization [180]. However, immunization is less beneficial for females who have already been infected with one of more of the HPV vaccine types.

All guidelines for HPV vaccination have, as target, the same age group for routine vaccination, but they differ in the catch-up age range. This is primarily due to cost-effectiveness analyses which show the benefit and cost effectiveness is lower when vaccination is given at older ages.

The United States Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP), the American Academy of Family Practice (AAFP), and the American College of Obstetricians and Gynecologists (ACOG) recommend the bivalent or quadrivalent HPV vaccines for females aged 11–12 for the prevention of cervical, vaginal, and vulvar cancer and the related precursor lesions caused by the HPV types targeted by these vaccines [79, 181].

The bivalent or quadrivalent vaccines can be administered to females as young as age 9. Catch-up vaccination is also recommended for females aged 13–26 years who have not been previously vaccinated or who have not completed their vaccine series [182].

The American Cancer Society (ACS) guidelines recommend that HPV vaccination should be routinely offered to females aged 11–12 years; immunization may begin at 9 years of age [183]. However, the ACS recommends catch-up vaccination for females aged 13–18 who have not been previously vaccinated or completed their vaccine series, as there is insufficient evidence to recommend for or against vaccination of females aged 19–26 years.

The World Health Organization (WHO) position paper suggests that girls within the age range of 9–13 years should be the primary target population for HPV

immunization [184]. Interest in HPV vaccine efficacy and safety in young males makes possible decrease in transmission of HPV infection to female sex partners.

In a placebo-controlled international trial, the efficacy of quadrivalent HPV vaccine was evaluated among 4065 males aged 16–26 [185]. The results demonstrated were: efficacy of immunization against the development of external genital lesions and persistence of HPV infection (by HPV 6, 11, 16, or 18 types) was 90% and 86%, respectively, among HPV-naïve males (no evidence of infection with the relevant HPV vaccine types at enrollment) who received all three doses of vaccine. In contrast, vaccine efficacy was significantly lower among the overall patient population with or without HPV infection at enrollment (66% for the prevention of external genital warts and 48% for the prevention of persistent HPV infection).

Cost-effectiveness analyses have suggested that male vaccination is less cost effective than female vaccination [186]. However, the overall cost effectiveness of male vaccination depends on a range of assumptions, such as vaccine efficacy, vaccine coverage of females, the range of health outcomes included, and the effect of HPV-associated diseases on quality of life [187]. For women and men, vaccination becomes increasingly less cost effective with increasing age.

Vaccination of pregnant females – Although neither HPV vaccine contains live virus (is not infectious), use in pregnancy is not recommended because of limited data on safety [181]. HPV vaccines are considered teratogenicity category B [79]. Lactating females can safely receive the immunization [79] series since subunit vaccines do not affect the safety of infant breastfeeding [188].

If a woman receives the HPV vaccine before she knows that she is pregnant she should be reassured that there is no evidence that this vaccine will harm the pregnancy [178]. However, females who have started the series, but become pregnant before completion of all three shots, may resume the series when postpartum.

Vaccination of immunosuppressed or immunocompromised hosts – Transplant recipients and HIV-infected patients, particularly those with low CD4 counts (<200 cells/mm<sup>3</sup>) are at risk for HPV-related disease.

HPV vaccine is recommended by the ACIP for persons who are immunocompromised as a result of infection, disease, or medications through age 26 years if they have not already received any or all vaccine doses [181].

### **23.5.4 Immunization Schedule**

Quadrivalent vaccine (Gardasil): administered in three doses at time 0, 2 and 6 months of follow-up.

Bivalent vaccine (Cervarix): administered in three doses at time 0, 1 and 6 months of follow-up.

The ACIP recommends that if the vaccination series is interrupted for any length of time, it can be resumed without restarting the series.

HPV vaccines have shown excellent duration of protection for the time periods through which they have been studied. However, the duration of protection after



immunization is unknown; to date, women have been protected during a mean follow-up time of 42 months after the first dose of quadrivalent HPV vaccine [189]. The precise level of antibody needed for protection against infection is also unknown.

Challenges for HPV vaccination include older age for vaccination, a three-dose regimen at a high cost relative to other childhood vaccines, and potential sociocultural concerns about HPV being a sexually transmitted disease [79]. The majority of CC cases occur in the developing world [79, 190] and patients in these nations are less likely to receive HPV vaccination. Despite its high cost relative to other childhood vaccines, in nations with high incidence, emerging models suggest that vaccination is cost-effective [79, 191].

## 23.6 HIV and Cervical Cancer

HIV testing should be recommended to women with newly diagnosed CC under age 50, particularly in women under age 30 or with widely advanced disease or unusual sites of metastases. In 1993 the Centers for Disease Control and Prevention (CDC) designated moderate and severe cervical intraepithelial neoplasia as conditions defining a stage of early symptomatic HIV infection (category B), and invasive CC as an acquired immunodeficiency (AIDS)-defining condition (category C) [192]. CC is now the most common AIDS-related malignancy in women at some centres in the United States [193]. Prevention of CC is an important part of care for women with HIV.

It is reported that the HPV point prevalence in HIV-positive women is as high as 60%, compared to about 30% in HIV-negative women [194]. HIV infected women are at risk of immune system impairment and immunosuppression is an important risk factor for development of CIN, probably because the weakened response of the immune system allows HPV to persist.

### 23.6.1 Pathophysiology

In HIV-infected women with no evidence of CIN on Pap smear and colposcopy and negative HPV testing, the probability of developing CIN is much greater than in women who are HIV-negative (20% vs. 5%). The strongest predictor of development of CIN in HIV-positive women is the degree of immunosuppression delineated by CD4 counts [195]. When matched for sexual behaviour, HIV-positive women have a one to twofold increase in HPV sero-prevalence compared to HIV-negative women.

The clearance of HPV in an HIV-positive individual correlates directly with the CD4 count. HPV DNA prevalence is as high as 85% in those with CD4 counts of 0–500 and as high as 70% in those with CD4 counts over 500. This is compared to

a range of 30–50% in HIV-negative women. Even with a normal CD4 count, HIV-positive women still have a twofold increase in incidence of HPV compared to HIV-negative women [195]. Infection of vaginal Langerhans cells (LC) by HIV is a primary mode of entry and propagation into systemic infection. LCs constitute an important local defense against HPV infection. The numbers of LCs are lowered significantly in patients with AIDS with a resultant decrease in their immunologic response to HPV.

HIV-infected women require regular periodic cervical Papanicolaou (Pap) testing. The CDC and the U.S. Preventative Services Task Force recommend cytologic screening as part of the initial evaluation when HIV is diagnosed. If the initial Pap smear is normal, additional evaluation should be repeated within 6 months. Thereafter women with normal Pap smears should be re-evaluated at least annually. Pap smears showing severe inflammation with reactive squamous cellular changes should be repeated within 3 months. Additional evaluation of HPV DNA, with a subsequent screening frequency of 6 months in women with detectable high-risk subtypes of HPV and yearly in those without high risk HPV, has been proposed as a more individualized screening algorithm. If a Pap smear shows squamous intraepithelial lesions or atypical squamous cells of undetermined significance, cervical colposcopic examination with directed biopsies of mucosal abnormalities is indicated.

Low-grade lesions (CIN1) are generally observed closely, and higher-grade lesions (CIN2–3) are generally treated. Initiation of cART and associated immune reconstitution has been associated with regression of lesions over time in certain cases, and may decrease the risk of recurrence. Treatment options for CIN include ablative therapy, loop excision of the transformation zone, or conization procedures, and should be individualized based on lesion size and location.

Invasive CC should largely be approached using principles of oncologic management that guide treatment in HIV-negative patients. The FIGO staging system, used for non-HIV-infected patients, is used in this population as well. More recently, PET-CT has been incorporated in the initial assessment of women with CC, largely because of the prognostic value of FDG-avid paraaortic lymph nodes. However, in women with HIV and CC, results should be interpreted with the understanding that uncontrolled HIV viremia is associated with lymph node [17] FDG-avidity. Treatment is based on clinical stage. There are no clinical trials specific to HIV-infected women with CC. In the absence of information to the contrary, HIV-positive women with CC should be treated in the same manner as those without HIV infection, with cART integrated into the overall treatment plan.

### ***23.6.2 HPV Vaccination and Its Effect on HIV-Positive Women***

In Phase 3 clinical trials, HPV vaccination has been shown to be effective in reducing the rate of HPV infection by over 90% by inducing a much higher antibody titer for almost 5 years, compared to the natural immune response [196]. None of these trials included women known to have HIV infection, and data demonstrating the

efficacy of HPV vaccines in HIV-positive women are lacking and uncertain. However, HPV vaccination is recommended by government organizations for this patient population.

Follow-up: HIV-infected women with CIN should be advised that recurrence is more frequent than in the general population and the risk of recurrence correlates inversely with the degree of immunosuppression. Recurrence rates are as high as 56%, and up to 87% in severely immunocompromised (CD4 lymphocyte count <200 cells/mL) women [197].

## 23.7 Cervical Cancer and Pregnancy

One percent of all patients with CC are pregnant at diagnosis. Most will present with abnormal cytology or abnormal vaginal bleeding. Overall, incidence of abnormal cytology in pregnancy is about 5%. The availability of cervical cytology in developed countries affords an opportunity to diagnose early dysplastic changes during pregnancy, which may contribute to a higher incidence (3:1) of stage I CC diagnosed during pregnancy compared to the nonpregnant state. The use of an endocervical brush is safe and can enhance the rate of optimal smears. Endocervical curettage is not recommended due to predisposition to premature rupture of membranes and bleeding.

### 23.7.1 *Diagnosis*

All abnormal cervical lesions during pregnancy require a biopsy. Colposcopy in pregnancy is used to rule out invasive disease. Colposcopic evaluation and directed biopsies are safe in pregnancy. Failure to visualize the entire squamocolumnar junction (SCJ) is not an indication to proceed to conisation during pregnancy, as most repeat colposcopies will be satisfactory due to eversion of the SCJ as the pregnancy progresses.

A diagnosis of CC during pregnancy requires a multidisciplinary approach involving gynaecologic and radiation oncologists, perinatologist, neonatologist, and psychologic counsellors. MRI can be used safely during pregnancy to evaluate spread of disease and lymph nodes [198].

### 23.7.2 *Management of Dysplasia*

The progression rate from dysplasia in pregnancy to higher-grade dysplasia in the postpartum period is less than 10%. Therefore, it is reasonable to manage abnormal cytology in pregnancy similarly to nonpregnant states. Given the low rate of progression and high reliability and safety of colposcopy, a conservative approach is

likely to be safe for the patient and the unborn child. Dysplasia diagnosed by colposcopy and biopsies in pregnancy should be followed conservatively with serial colposcopic examinations every 8 weeks and managed definitively in the postpartum period.

### **23.7.3 Conization During Pregnancy**

If conization is indicated during pregnancy, a cold knife technique may be the preferred method and second trimester is the best period for that.

### **23.7.4 Management of Invasive Cancers During Pregnancy Surgery**

Over 70% of CC in pregnancy present as stage I disease and have an excellent survival rate. Stage, tumour size, nodal status, gestational age, and the patient's desire to maintain the pregnancy are key elements in making therapeutic decisions. Treatment options can be separated according to gestational age of less than 20 or more than 20 weeks [79].

Invasive disease diagnosed in a pregnant patient of less than 20 weeks gestation should generally be managed immediately, resulting in loss of the foetus. However, there are reports of delaying treatment until foetal maturity without harm to the mother or the foetus. Most of the reported cases of delay in treatment were stage I disease. The delay of treatment ranged from 3 to 32 weeks. The overall mortality is about 5–6% with a similar recurrence rate. These data are limited by small numbers of patients but are reassuring when considering a delay in treatment. This approach is appropriate only in selected well-counselled patients with early-stage, small-volume disease [79].

Patients choosing to delay definitive surgical treatment of stage I disease until after delivery may safely undergo appropriate surgical treatment.

For stage I disease, surgery can be safely performed prior to 20 weeks with foetus in situ or as a planned procedure after caesarean section in the third trimester after documentation of foetal lung maturity. Excellent oncologic outcomes are generally obtained. There are scattered case reports of treatment of locally advanced disease with neoadjuvant chemotherapy using cisplatin alone or in combination with paclitaxel followed by radical surgery after delivery with good results, although there are no large datasets to support routine use [199]. Neoadjuvant chemotherapy can be considered after extensive discussion with mother and family if there is strong desire to maintain the pregnancy despite the diagnosis. The use of these drugs appears to be safe during pregnancy after first trimester but caution and a careful, multidisciplinary approach are necessary.

### **23.7.5 Radiotherapy**

Most reports of RT or chemoradiation for CC during pregnancy are in patients with locally advanced disease. NCCN guidelines suggest that patients with early-stage disease have radical hysterectomy and node dissection instead of radiation therapy in an effort to avoid radiation fibrosis and to preserve ovarian function [200].

Although experience is limited with chemoradiation in pregnancy, it seems to be feasible and safe. If radiation therapy is used in the postpartum setting, it should begin within 3 weeks after uterine involution.

### **23.7.6 Neoadjuvant Chemotherapy in Pregnancy**

Neoadjuvant chemotherapy in pregnant women with CC is guided by gestational age at diagnosis, the woman's desire to maintain the pregnancy, stage of disease, lymph node involvement, and histology. Although rare histologic subtypes such as small cell carcinoma have a poor prognosis and pregnancy termination with immediate treatment is recommended, conventional histologic subtypes including squamous cell, adenocarcinoma, and adenosquamous may be managed without pregnancy termination depending on stage and lymph node involvement [201].

In 2009, a French Working Group and a European International Consensus Meeting published separate guidelines with specific management recommendations [202]. These guidelines differed slightly. However, they both agreed that for women with CC who wish to maintain their pregnancy, proper staging with the determination of lymph node involvement was necessary prior to the determination of treatment. Women with stage IA disease and no lymph node involvement have an excellent prognosis and delayed treatment until foetal maturation is the standard of care. Women with stage IB1 disease and no lymph node involvement may undergo a radiation therapy or proceed with neoadjuvant chemotherapy to commence after the first trimester of pregnancy and continue until foetal maturation. Women with stage IB1 with lymph node involvement and those with stage IB2 or greater disease may also receive neoadjuvant chemotherapy to allow for foetal maturation following the first trimester of pregnancy [201]. Although the literature is limited and long-term follow-up lacking, neoadjuvant platinum-based chemotherapy in pregnant women with cervical cancer appears to be feasible and safe for both the mother and infant.

### **23.7.7 Radical Trachelectomy During Pregnancy**

Vaginal or abdominal trachelectomy and cerclage placement along with laparoscopic or pelvic lymphadenectomy is an option for treatment of stage I CCs less than 2 cm in women interested in preserving pregnancy and fertility [203].

## 23.8 Fertility Preservation in Female Adolescent and Young Adult

The majority of epithelial genital tract tumors diagnosed in female adolescent and young adult are carcinomas of the uterine cervix, accounting for 22% of the genital tumours [204].

An important issue for adolescent and young adult with early stage CC is fertility preservation. The standard treatment ranges from simple hysterectomy (stage IA1) to radical hysterectomy and pelvic lymphadenectomy (stages IA2-IB1). Notwithstanding, the remarkable survival rates for early stage tumours and the late childbearing in the modern society result in more CC patients who desire to maintain their fertility. In this scenario, fertility-sparing approaches are available for part of cases [205].

Cervical conization is an attainable treatment for stage IA1 carcinomas and has been suggested as a conservative surgical alternative and fertility sparing approach. The absence of lymphovascular involvement at the pathological examination with negative margins and normal endocervical curettage are the prerequisites for conization [205]. When the patient desires to preserve fertility, in the presence of lymphovascular involvement, radical trachelectomy with pelvic node dissection is the treatment of choice [206]. In the published series, no differences in survival rates have been reported among conization and simple hysterectomy [85, 207] and in terms of obstetrical outcome, conization is associated with an increased risk of pre-term delivery [207].

A high incidence of pelvic lymph node metastases is detected at stages IA2-IB1 and pelvic node dissection is mandatory. As fertility sparing treatment, radical trachelectomy with lymphadenectomy has become a surgical alternative. Usually, pelvic lymph node dissection is performed before trachelectomy. Nodes from the external, internal iliac and obturator chain are removed and evaluated by a frozen section. If lymph nodes are negative for metastasis, trachelectomy is performed; if lymph nodes are positive for tumour cells, definitive chemotherapy and radiotherapy is the treatment of choice [205]. Trachelectomy is generally accompanied by cervical cerclage, which is also recommended in the second trimester for the patients who become pregnant [205].

Good gynaecological, oncological and obstetrical results have been reported with trachelectomy. One centimetre of cervical stroma is required to decrease the chance of premature delivery [208, 209] and neoadjuvant chemotherapy can be offered in selected cases where the margins are less than 1 cm [205].

No significant differences have been shown comparing intraoperative and post-operative complications of trachelectomy and radical hysterectomy or in survival rates [205].

Pregnancies after trachelectomy are considered as high risk. Second trimester miscarriage and premature rupture of membrane and premature labour are common complications [205, 210]. Chorioamnionitis can be a result of the shortened cervix

[210] and infertility has been reported in 25–30% of patients after trachelectomy due to cervical stenosis, decreased cervical mucus, and subclinical salpingitis [211].

For the patients with positive or close resection margins, positive lymph nodes, parametrial involvement or advanced stage (IB2-IVA) adjuvant or definitive chemoradiotherapy is needed. Ovarian transposition, not only for preservation of fertility but also to prevent premature menopause, can be performed to avoid damage of ovarian tissue when radiation is needed [212].

### Clinical Case

Patient with 32 years old, white, ECOG 1, complaining of transvaginal bleeding was diagnosed with a cervical lesion of 5 cm. She was referred to a tertiary center where she was assisted by a multidisciplinary team. The first evaluation was made by a gynecologic oncologist who performed a pelvic examination and found a lesion of 5 cm in the cervix that extended thru the left parametrium. Biopsy showed a grade 3 squamous cell carcinoma.

After the diagnosis of cervical carcinoma, the patient performed a PET-CT and a pelvic MRI that confirmed a lesion in the cervix with suspected right pelvic lymph node metastasis, without contrast uptake in the para-aortic region. Blood samples showed normal renal and hepatic function and no anemia.

The multidisciplinary team proposed treatment with concomitant cisplatin (40 mg/m<sup>2</sup> weekly for 6 weeks) and pelvic radiotherapy followed by brachytherapy, aiming to achieve 85 Gy in less than 56 days.

After 16 months of follow-up, a right supraclavicular node enlargement was noted on her physical examination. Another PET-CT was performed that showed uptake of the para-aortic, mediastinal and right supraclavicular nodes. A fine needle aspiration of the supraclavicular node confirmed metastatic squamous cell carcinoma.

The patient had no contraindication for bevacizumab containing regimes and a combo of paclitaxel, cisplatin and bevacizumab was initiated. She received 8 cycles of chemotherapy with a partial response. After 4 for months of chemotherapy she had progressive disease in lungs and mediastinal lymph nodes. Her ECOG was 3 and best supportive care was given until she died.

### Questions

1. A 45 y/o woman with squamous cell cervical carcinoma, 6 cm of diameter, with no parametrial invasion (FIGO IB2). What baseline investigations would you order next as part of her initial work-up to best delineate your treatment plan?
  - (a) Chest X-Ray, intravenous pyelography and/or pelvic ultrasound, blood work (blood count with renal and hepatic function tests), cystoscopy/proctoscopy (if clinically indicated)
  - (b) **Pelvic MRI + PET-CT + Blood work + cystoscopy/proctoscopy (if clinically indicated)**
  - (c) Physical exam only + blood work

- (d) CT scans of abdomen and pelvis + Chest CT or XR + Blood work + cystoscopy/proctoscopy (if clinically indicated)
- (e) Other

Answer: FIGO staging system utilizes physical examination and basic imaging to stage patients. Another important part of the staging is the assessment of lymph node status and distant metastasis. For these purposes, PET-CT and pelvic MRI are important imaging studies that can guide us to a better treating planning, for example extending radiation fields to para-aortic region.

2. A 56 y/o woman with adenocarcinoma of the cervix, FIGO stage IA1 was treated with conization. At final pathology review she had focal positive margins and positive LVSI. What is the next step?
  - (a) Observation
  - (b) **Modified radical hysterectomy + pelvic lymph node assessment**
  - (c) Repeat conization to get clear margins
  - (d) Brachytherapy
  - (e) Other

Answer: Based on the most recent guidelines (NCCN guidelines for Cervical Cancer Version 1.2018), patients with stage IA with positive LVSI should be offered pelvic lymph node assessment since the risk of metastasis increase when LVSI is positive.

3. A 28 y/o woman presents with a cervical squamous cell carcinoma stage IB1 (2.0 cm). She desires pregnancy in the near future. After staging work up excludes metastases what would you propose?
  - (a) Conization with negative margins
  - (b) Conization with negative margins + pelvic lymphadenectomy
  - (c) **Radical trachelectomy + pelvic lymphadenectomy +/- para-aortic dissection**
  - (d) Radical Hysterectomy with lymph node assessment (I wouldn't propose fertility sparing surgery because I believe it is investigational and I don't want to compromise the oncologic outcome).
  - (e) Radical Hysterectomy with lymph node assessment because I don't have expertise to perform trachelectomy + lymph node assessment

Answer: Patients who desire to preserve fertility with tumors less or equal to 2 cm can be safely treated with trachelectomy and pelvic lymphadenectomy

4. A 55 y/o woman underwent a radical hysterectomy + pelvic node dissection together. Final path review showed a cervical squamous tumor 2.8 × 2.5 cm with 22 pelvic lymph nodes negative, clear margins, negative LVSI and a focal positive left parametrium. What would you propose?
  - (a) Observation
  - (b) Pelvic Radiation Therapy + Brachytherapy



- (c) **Pelvic Radiation Therapy + Concomitant cisplatin containing chemotherapy**
- (d) Brachytherapy alone
- (e) Other

Answer: Based on GOG 109/RTOG 91–12 patients with post-operative positive margins, positive parametrium or lymph node metastasis had a better survival with concomitant treatment compared to pelvic radiation alone.

5. A 52 y/o woman was diagnosed with squamous cell carcinoma of the cervix was staged as FIGO IB1 and underwent radical hysterectomy and pelvic lymph node dissection (histopathology showed a 2.5 cm squamous cell carcinoma with negative LVSI with cervical stromal invasion of the inner one-third of the cervix, negative pelvic nodes, no parametrial invasion, and clear margins). What would you propose next?
- (a) Adjuvant external beam radiation
  - (b) Adjuvant external beam radiation with brachytherapy
  - (c) Brachytherapy
  - (d) **Surveillance**

Answer: Patient has no criteria for adjuvant treatment based on GOG 92 or GOG109 and this approach is in line with current guidelines (NCCN guidelines for Cervical Cancer Version I.2018)

6. A 45 y/o woman with squamous cell carcinoma of the cervix was staged as FIGO IB2 (6 cm tumor). How would you treat her?
- (a) Radical hysterectomy followed by radiation therapy depending on pathological results.
  - (b) **Concurrent chemotherapy and radiation therapy including both external beam and brachytherapy.**
  - (c) Concurrent chemotherapy and radiation therapy (external beam only) followed by surgery
  - (d) Neoadjuvant chemotherapy followed by surgery and radiation if indicated by pathological results.

Answer: The standard treatment for patients with stage FIGO IB2 is concomitant treatment followed by brachytherapy based on RTOG 90-01 and GOG 123

7. A 52 y/o woman presents with a 3 cm squamous cell carcinoma of the cervix compromising the upper third of the vagina. She was staged as FIGO IIA. What would you propose?
- (a) Pelvic radiation therapy with concomitant cisplatin based regimen followed by brachytherapy
  - (b) Neoadjuvant chemotherapy followed by radical hysterectomy + pelvic and paraortic lymph node dissection

(c) **Radical hysterectomy + pelvic lymph node dissection (+/- paraortic sample) followed by adjuvant therapy depending on the pathology results.**

(d) Other

Answer: Based on NCCN guidelines for Cervical Cancer Version I.2018, the best approach for patients with stage FIGO IIA1 is surgery. Indeed, studies like RTOG 90-01 did not include patients with FIGO IIA1.

8. A 35 y/o patient presents after work-up with a FIGO IIB cervical squamous cell carcinoma of the cervix. How should this patient best be treated?

(a) Neoadjuvant Chemotherapy plus Radical Hysterectomy + lymph node assessment (pelvic +/- para-aortic)

(b) **Concomitant chemotherapy (cisplatin-containing) with pelvic irradiation followed by brachytherapy**

(c) Pelvic radiation therapy followed by brachytherapy

(d) Radical Surgery

(e) Other

Answer: Based on randomized studies (GOG 85, GOG 120 and RTOG 90-01) and guidelines (NCCN), the best approach for patients with stage IIB cervical cancer is the combination of chemotherapy and radiotherapy followed by brachytherapy.

9. A 38 y/o woman with FIGO stage IIIB squamous cell carcinoma of the cervix is found on work-up to have suspicious para-aortic lymph nodes. Para-aortic fine needle biopsy confirms metastatic disease. How would you treat this patient?

(a) Palliative chemotherapy

(b) Pelvic and para-aortic radiation therapy

(c) **Pelvic and extended field para-aortic radiation therapy concomitant with cisplatin-containing chemotherapy**

(d) Best supportive care

(e) Other

Answer: Patients with para-aortic metastasis have worse prognosis but they can still have long- term survival. The most accepted approach in this scenario is the combined treatment with extended para-aortic irradiation as supported by the NCCN guidelines for Cervical Cancer Version I.2018

10. A 49 y/o woman was treated with chemoradiation for a cervical tumor FIGO IIIB in 2013. Presently, her imaging shows progressive disease in the para-aortic and mediastinal lymph nodes and few asymptomatic lung metastases. Her performance status is ECOG 1. What treatment would you offer?

(a) Best supportive care

(b) Single agent chemotherapy (eg cisplatin)

- (c) Platinum + Paclitaxel because you believe that bevacizumab does not add worthwhile benefit
- (d) Platinum + Paclitaxel because we do not have bevacizumab available
- (e) **Platinum + Paclitaxel + Bevacizumab**

Answer: Until recently, patients with metastatic disease were treated with a doublet of platinum and taxane based on GOG 204. Since the publication of GOG 240 which compared the standard combo with addition of bevacizumab and showed a gain in overall survival for the experimental arm, this regime became the gold standard in treating metastatic cervical cancer.

### Discursive Questions and comments

1. What exams should be done in order to stage patients with locally advanced cervical cancers (FIGO IB2 to Iva)?

FIGO staging system consists basically on clinical and limited image exams as x-rays, ultrasound and intravenous pyelography. It is well known that accuracy of clinical staging is low compared to surgical staging. FIGO system does not account for one of the most important prognostic factors in cervical cancer: the status of pelvic and paraortic lymph nodes. Staging lymphadenectomy is the gold standard to assess metastatic disease in lymph nodes and PET-CT is the most sensitive image (compared to CT and MRI). PET-CT should be performed since it can change radiotherapy fields or even change therapeutic planning if it finds distant metastatic disease. Regarding local spread, MRI is considered the best exam to assess local extension. In one study performed by GOG/ACRIN, MRI was more sensitive and had a better negative predictive value to show parametrial extension when compared to CT scans and physical exam.

2. What is the most appropriate therapy in metastatic, persistent or recurrent cervical cancer?

Cisplatin, alone or in doublets, was for a long time the standard of care for patients with recurrent, persistent or metastatic cervical cancer. The first study to show superiority against cisplatin alone was the association with topotecan, which demonstrated a better progression free and overall survival. GOG 204 compared 4 different doublets and cisplatin plus paclitaxel was considered the new standard. Recently, bevacizumab was studied in combination of cisplatin and paclitaxel or topotecan and paclitaxel in GOG 240. In this study, the addition of antiangiogenic demonstrated superior overall and progression free survival.

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# Chapter 24

## Vaginal Cancer



Michail Nikolaou

**Abstract** The vagina is a muscular part of the female genital tract, and it extends from the vulva to the cervix. Its length is approximately 7.5 cm, and anatomically, it is found between the bladder and the rectum. The wall of the vagina has three layers: mucosa, muscularis and adventitia. The mucosa is formed by squamous epithelium [Nikolaou M. Vaginal cancer, international manual of oncology practice. Springer, Cham. [https://doi.org/10.1007/978-3-319-21683-6\\_20](https://doi.org/10.1007/978-3-319-21683-6_20), 2015]. The upper third of the vagina is the part in which cancer is most common (56%), secondarily the lower third (31%) and lastly the middle third (13%) [Slomovitz BM, Coleman RL. Invasive cancer of the vagina. In: DiSaia PJ, Creasman WT (eds) Clinical gynecologic oncology, 8th edn. Elsevier Saunders, Philadelphia, pp 245–259, 2012]. The upper two-thirds of the vagina drain mainly into the pelvic lymph nodes, in contrast with the lower third that drains into the inguinal lymph nodes. This knowledge helps in understanding the mechanism of metastasis and the choice of the best treatment in a given case [Monaghan JM. Invasive tumor of vagina: clinical features and management. In: Coppleson M (ed) Gynecologic oncology. Churchill Livingstone, Edinburgh, p 506, 1992].

**Keywords** Vaginal Cancer · Vagina · Cancer

### 24.1 Anatomy

The vagina is a muscular part of the female genital tract, and it extends from the vulva to the cervix. Its length is approximately 7.5 cm, and anatomically, it is found between the bladder and the rectum. The wall of the vagina has three layers: mucosa, muscularis and adventitia. The mucosa is formed by squamous epithelium [1]. The upper third of the vagina is the part in which cancer is most common (56%), secondarily the lower third (31%) and lastly the middle third (13%) [2]. The upper two-thirds of the vagina drain mainly into the pelvic lymph nodes, in contrast with the lower third that

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drains into the inguinal lymph nodes. This knowledge helps in understanding the mechanism of metastasis and the choice of the best treatment in a given case [3].

## 24.2 Epidemiology

Vaginal cancer is a rare cancer (1–2% of all female genital cancers), but there are many types of disease. In total, 92% of the patients are diagnosed with in situ or invasive squamous cell carcinoma (SCC) or adenocarcinomas, 4% with melanomas, 3% with sarcomas and 1% with other types of cancers. Of all vaginal cancers, in situ carcinoma accounts for 28%, and invasive carcinomas account for 66%; SCC accounts for 79%, and adenocarcinoma accounts for 14% according to the National Cancer Data Base (NCDB) report [4]. Vaginal cancer is associated with advanced age and is more common in the 6th and 7th decades of life. Younger patients tend to present with adenocarcinoma. Currently, human Papillomavirus (HPV) infection in young women marks a critical therapeutic point [1].

## 24.3 Risk Factors

There are many risk factors for vaginal cancer, one of which is HPV infection. It is now known that 60% of invasive SCC of the vagina is HPV related. HPV-positive lesions were found in 56.0% of vaginal Low-grade Squamous Intraepithelial Lesion (LSIL) and in 78.3% of vaginal High-grade Squamous Intraepithelial Lesion (HSIL) [5]. Other potential risk factors include chronic conditions, smoking, sexual debut before the age of 17 years, low socioeconomic status, history of genital warts, five or more sexual partners, prior cervical cancer or radiotherapy in the pelvis, immunosuppression and prior hysterectomy or abnormal cytology (vulvar intraepithelial neoplasia – VIN, cervical intraepithelial neoplasia – CIN and vaginal intraepithelial neoplasia – VAIN) [6–19].

From approximately 1940–1971, gynaecologists used the drug Diethylstilbestrol (DES) to avoid pregnancy complications and losses. When DES was taken by pregnant women, it was shown to cause a rare vaginal tumour in the fetus during the adulthood. The majority of cases involved the anterior upper third of the vagina wall, and the mean age at diagnosis in the DES-exposed patients was 19 years [20].

## 24.4 Signs and Symptoms

Vaginal bleeding is the most common symptom for vaginal cancer. Other signs and symptoms are pelvic pain, dysuria and a mass with abnormal cytology. In total, 10–20% of the patients are without symptoms. A biopsy is needed for diagnosis, with cytological evaluation and physical examination with digital palpation. It is recommended to perform the last examination under anaesthesia if the patient is in great discomfort [9].

## 24.5 Stage

There are two staging systems used for vaginal cancer. The American Joint Commission on Cancer classifications (AJCC) and the International Federation of Gynaecology and Obstetrics (FIGO) Tables 24.1 and 24.2 [21, 22].

**Table 24.1** TNM and FIGO staging for vaginal cancer

<i>TNM</i>	<i>FIGO</i>	<i>Definition</i>
Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of a primary tumor
Tis		Carcinoma in situ (pre-invasive)
T1	I	Tumor confined to the vagina
T2	II	Tumor invades paravaginal tissues but does not extend to pelvic wall
T3	III	Tumor extends to pelvic wall
T4	IVA	Tumor invades mucosa of the rectum or bladder or shows direct extension beyond the true pelvis
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	III	Regional (pelvic or inguinal) lymph node metastasis
Distant metastasis (M)		
M0		No distant metastasis
M1	IVB	Distant metastasis

**Table 24.2** Anatomic stage – prognostic groups

Stage	TNM		
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1–T3 T3	N1 N0	M0
IVA	T4	any N	M0
IVB	any T	any N	M1

In the NCDB, the 5-year survival rates are as follows:

Stage 0 (in situ) = 96%

Stage I = 73%

Stage II = 58%

Stage III and IV = 36%

## 24.6 Pathologic Classification

1. The most common pathologic type is Squamous Cell Carcinoma (SCC), comprising approximately 70–80% of vaginal cancers [23]. In total, 80% of the cancers are HPV related [24], and the most common is type 16, which accounts for 33–56% of cases [25]. There are five histological subtypes in SCC: keratinizing, non-keratinizing, basaloid, verrucous and warty. HPV appears more often in the non-keratinizing, basaloid and warty forms [26].
2. Glandular tumours are similar to Clear Cell Carcinoma (CCC) of the ovary or endometrium cancer and are commonly associated with vaginal adenosis [27]. This type has a worse prognosis than other types of vaginal cancers. The 5-year survival rate is 34%, compared to 58% for SCC and 93% for DES-associated Clear Cell Carcinoma [23, 28].
3. Primary vaginal adenocarcinoma (endometrial endometrioid adenocarcinomas, mucinous adenocarcinoma, serous adenocarcinoma and mesonephric adenocarcinoma) has been reported.
4. Adenosquamous cancer comprises 2% of vaginal cancers [27]. These tumours are a mix of glandular and squamous components, lack endometriosis or adenosis and have a more aggressive biology.
5. Primary vaginal Small Cell Carcinoma (Neuroendocrine) is a very aggressive and rare tumour with poor prognosis. These tumours usually express Synaptophysin, a neuroendocrine marker [29].
6. Vaginal paraganglioma is another very rare epithelioid tumour [30].
7. Mixed epithelial and mesenchymal tumours, such as Carcinosarcoma/Malignant Mixed Müllerian tumour (MMMT), have been reported to be SCC with an epithelial component [31].
8. Sarcomas represent approximately 3% of primary vaginal cancers. Two of the main tumours represented are Rhabdomyosarcoma and Leiomyosarcoma.
9. Angiomyofibroblastoma and myofibroblastoma are benign pathology types and are associated with mesenchymal tumours that may occur in the vulva or vagina and may be related to Tamoxifen treatment and be distinguished from aggressive Angiomyxoma [32, 33].
10. Primary vaginal malignant melanomas comprise 3–8% of primary vaginal cancers [27]. Prognosis is worse than cutaneous melanoma, with 5-year survival rates of 5–20% [23, 27].
11. Extragonadal Yolk Sac Tumours (YSTs) are germ cell tumours largely affecting children younger than 3 years and have been reported in the vagina as the primary site of a rare paediatric tumour. Correct diagnosis is critical because these tumours respond to platinum-based chemotherapy (Cisplatin, Etoposide, and Bleomycin), and surgical treatment may not be necessary [34]. Serum  $\alpha$ -fetoprotein (aFP) is a sensitive tumour marker for diagnosis and treatment, and it is elevated in all patients [35].
12. Primary Non-Hodgkin Lymphoma (NHL) is rare, accounting for less than 1% of extra-nodal lymphomas [36].
13. Plasmacytoma and eosinophilic granuloma are very rare tumours, and there are a few reports in the medical bibliography [27].

## 24.7 Prognostic Factors

Lesion size may be a prognostic factor with an adverse impact. The increasing size has been associated with worse overall survival (OS) in several studies [11, 13]. The location has also played a controversial role. Decreased recurrence rates and better OS have been shown with cancers involving the distal half or those involving the entire length of the vagina, according to several studies [11, 19]. The grade stage and involving lymph nodes (metastasis) at diagnosis are important predictive markers for poor prognosis. Additionally, the histological type and grade are a significant predictive marker [13]. Overexpression of HER2-neu oncogenes of the lower genital tract is a rare situation and is associated with aggressive biological behaviour [37]. In contrast, overexpression of p53 protein (wild type – WT) is associated with a more favourable prognosis [38]. The performance status (PS) and age have also been reported as prognostic factors, with increasing age correlating with poorer survival [19].

## 24.8 Management and Treatment Options

Vaginal cancer is a rare tumour, and for this reason, no randomized controlled trials exist, and our data are extracted from retrospective studies. Usually, patients with vaginal cancer are elderly, and this significantly determines the treatment they will receive. Even the choice of surgical method depends not only on the site of the tumour but also on the age of the patient, and in several cases the treatment of choice is radiotherapy because of the significant reduction in quality of life after an extensive surgery [1]. Many are at a disadvantage in choosing surgery versus radiotherapy due to complications such as damage to the rectum, urinary bladder and fistulation after surgical excision. In contrast, the greatest benefit of radiotherapy is preserving the function of adjacent organs [39, 40]. Additionally, the histological type plays an important role since in patients, with stage I and II adenocarcinoma, especially clear-cell adenocarcinoma, having poor sensitivity to radiotherapy, and surgical therapy is preferred [2, 41]. The overall 5-year survival rate with radiotherapy is 70–80% in stage I, 50–70% in stage II, 30–50% in stage III and 0–20% in stage IV and the pelvic control rate is 80–90% in stage I, 50–70% in stage II, 50–60% in stage III and 30% in stage IV [42–47].

Groups from the Society of Gynaecologist Oncologists in 1998 to the Japan Society of Gynaecologic Oncology in 2015 have attempted to define guidelines, but the optimal approach for each stage is not well-defined. A combination of radiotherapy and limited surgery has been suggested to improve outcomes per case [48]. The use of chemotherapy is based on phase II trials of various monotherapies or extrapolated from cervical cancer, which has a similar biology. For stage III and IV, chemotherapy alone offers limited benefit in the management of disease. Usually, healthier and younger patients with better performance statuses are eligible for radical surgery, while older patients with comorbidity are preferred for radiotherapy [49].

Table 24.3 lists the proposed treatment options per stage in patients with vaginal cancer.

**Table 24.3** Proposed therapeutic options per stage in vaginal cancer

Clinical stage	Clinicopathological treatment plan findings	Treatment plan	or	or	or	Comments
VAIN	LSIL HSIL	Follow up Resection	or	Laser vaporization	or	Surgery (local, partial or total Vaginectomy) loop electrosurgical excision procedure (LEEP) have great risk of injury to the rectum or urinary bladder and is not recommended [50]
Stage I	Tumor thickness $\leq 5$ mm	Brachytherapy (the area of tumor involvement 60 Gy in one dose and an additional mucosal dose of 20–30 Gy [51])	or	External-beam radiation therapy + Brachytherapy	or	Surgery (Partial vaginectomy with a pelvic lymphadenectomy, or radical hysterectomy and pelvic lymphadenectomy)
	Tumor thickness $> 5$ mm	External-beam radiation therapy + Brachytherapy				Surgery (Partial vaginectomy with a pelvic lymphadenectomy, or radical hysterectomy and pelvic lymphadenectomy)

<p>Stage II</p>		<p>External-beam radiation therapy + Brachytherapy</p>	<p>External-beam radiation therapy</p>	<p>Surgery (Partial vaginectomy with a pelvic lymphadenectomy, or radical hysterectomy and pelvic lymphadenectomy)</p>		<p>Stage IIA patients have more advanced paravaginal disease without extensive parametrial infiltration. Stage IIB patients with more extensive parametrial infiltration to deliver a total tumor dose of 75–80 Gy to the vaginal tumor [11, 19, 52]</p>
<p>Stage III</p>		<p>External-beam radiation therapy + Brachytherapy</p>	<p>External-beam radiation therapy</p>	<p>Surgery (Radical hysterectomy and pelvic lymphadenectomy)</p>	<p>CCRT for stage III the control rate of pelvis is low with 70–80% of the patients have persistent or recurrent disease in spite of Brachytherapy and External-beam radiation therapy. Added concurrent chemotherapy with 5-FU, Cisplatin or Mitomycin-C have shown promise outcomes. Cisplatin was the best drug with improve the radiation sensitivity [53]</p>	<p>For stage III chemotherapy alone offer little benefit in the management of disease</p>

(continued)

**Table 24.3** (continued)

Clinical stage	Clinicopathological treatment plan findings	Treatment plan	or	External-beam radiation therapy	or	Pelvic Exenteration	or	CCRT for stage IV the control rate of pelvis is low with 70–80% of the patients have persistent or recurrent disease in spite of Brachytherapy and External-beam radiation therapy. Added concurrent chemotherapy with 5-FU, Cisplatin or Mitomycin-C have shown promise outcomes. Cisplatin was the best drug with improve the radiation sensitivity [53]	Comments
Stage IV	Stage IV A	External-beam radiation therapy + Brachytherapy	or	External-beam radiation therapy	or	Pelvic Exenteration	or	CCRT for stage IV the control rate of pelvis is low with 70–80% of the patients have persistent or recurrent disease in spite of Brachytherapy and External-beam radiation therapy. Added concurrent chemotherapy with 5-FU, Cisplatin or Mitomycin-C have shown promise outcomes. Cisplatin was the best drug with improve the radiation sensitivity [53]	For stage IV chemotherapy alone offer little benefit in the management of disease
	Stage IV B	Chemotherapy	or	Clinical Trial	or	BSC			

*LSIL* Low-grade Squamous Intraepithelial Lesion  
*HSIL* High-grade Squamous Intraepithelial Lesion  
*CCRT* Concurrent Chemo-radiotherapy  
*BSC* Best Supportive Care

## 24.9 Complications

A major problem that needs to be managed in a patient with vaginal cancer is the side effects from cancer itself, as well as those from surgery or from radiation therapy. Vaginal atrophy, fibrosis and stenosis are the most common problems. The anatomical proximity of the vagina to genitourinary tracts and the lower gastrointestinal system increases the degree of risk in each operation [54]. For example, the Loop Electrosurgical Excision Procedure (LEEP) has a great risk of injury to the rectum or urinary bladder and is not recommended [50]. Grade 3–4 adverse events (AE) after radiotherapy are reported in approximately 13–17% of cases and can even occur many years after treatment. Many patients had side effects such as urethral stenosis, haemorrhagic cystitis, vesicovaginal fistula, rectovaginal fistula, gastrointestinal obstruction or ileus and radiation proctitis immediately after radiotherapy or after several years [42, 44]. The probability of serious side effects and patients' quality of life is a relationship that should be constantly reassessed.

## 24.10 Primary Melanoma of the Vagina

Primary melanoma of the vagina (PMV) is a very rare type of tumour in the female genital tract. Three cases per 10,000,000 women per year is the incidence, and it is diagnosed in elderly women. Advanced stage, early recurrence and a poor prognosis are the main features of the disease [55–57]. The median overall survival (mOS) was 10 months, and the 5-year overall survival rate is approximately 20%, compared to approximately 80% for those with cutaneous melanoma [55–58]. At the same time, other important differences are recognized, such as the molecular characteristics. Cutaneous melanoma in up to 66% of cases have mutations in the BRAF proto-oncogene, whereas they are not observed in primary melanoma of the vagina. Additionally, vaginal and vulvar melanoma differ in their molecular characteristics regarding cutaneous melanoma in mast/stem cell growth factor receptor CD117 (KIT) mutations [59, 60]. The therapeutic targeting of molecular pathways such as BRAF, KIT, NRAS, PD-1, and CTLA-4 has not been established because patients with primary melanoma of the vagina are too small in number to allow large clinical trials and ensure safe outcomes [61]. For unresectable, metastatic and recurrent disease, chemotherapy with Dacarbazine is mostly used, while at the same time, immunotherapy with Interferon-alpha (INF-a), Interleukin (IL) and with novel drugs such as immune checkpoint inhibitors (Nivolumab, Pembrolizumab and Ipilimumab) have produced controversial results and often non-evaluable data in the medical literature [62, 63]. Additionally, the role of adjuvant radiotherapy is unclear, since it failed to result in a significant OS advantage compared to surgery alone [64].



## 24.11 Vaginal Sarcoma

There are many types of vaginal sarcoma, such as Rhabdomyosarcoma, Leiomyosarcoma, Mixed epithelial and mesenchymal tumours such as Carcinosarcoma – Malignant Mixed Müllerian tumour (MMMT), Angiomyxoma and Extragenital Yolk Sac tumours [23, 27, 32, 33]. They are very rare, making up approximately 2–3% of all vaginal cancers, and there are 50 cases of vaginal leiomyosarcoma reported in the medical literature. The 5-year overall survival rate is 17% in patients with Malignant Mixed Müllerian tumours and 36% in those with leiomyosarcoma [65].

The best chance for cure from vaginal sarcoma may be pelvic exenteration, because smaller surgical resections often lead to relapse and the disease is chemoresistant [4]. The role of adjuvant radiotherapy or chemotherapy is unclear. Cisplatin, Paclitaxel, Doxorubicin and Ifosfamide were found to be active, but it is unclear whether combinations of them are better than Ifosfamide alone [66, 67]. Because of the scarcity of the disease, there is no strong medical data, and it is often necessary to personalize the treatment based on the size, location, and clinical stage. Patients with advanced disease are recommended to receive chemo-radiation rather than radiotherapy only [68, 69].

## 24.12 Non-Hodgkin Lymphoma of Vagina

Primary Non-Hodgkin Lymphoma of Vagina (NHL) is a systemic disease, and for this reason, surgery should be avoided. After biopsy and histopathological identification, it is necessary to administer chemotherapy with CHOP: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone, or BACOP: Bleomycin, Adriamycin, Cyclophosphamide, Vincristine and Prednisone, or with combination chemo-radiotherapy, depending on the disease stage [36, 70].

## 24.13 Future Therapeutic Approach

Kallikrein-related peptidase 5 (KLK5) is expressed with other Kallikreins in all stratified epithelia, such as the vagina, indicating a possible role in differentiation. KLK5 may play a role in vaginal cancer development. Klk5<sup>-/-</sup> mice are prone to develop vaginal cancer when exposed to 7,12-dimethylbenz[a]anthracene. It has been found that the enhanced of Klk5<sup>-/-</sup> caused activation of Nf- $\kappa$ b, and this led to apoptosis of mutated vaginal cells. By extension, KLK5 may be a suppressor of vaginal tumours [71]. Further study may reveal significant data in the treatment of these tumours.

Additionally, the CheckMate 358 clinical trial (NCT02488759), a phase I/II study from October 2015 to February 2016, studied the administration of 240 mg of Nivolumab every 2 weeks after fewer than two prior systemic therapies for relapsed/metastatic disease in 24 patients. Nineteen of them had cervical and five had vaginal or vulvar cancer, and the median age was 51 years. Primary endpoints were safety and objective response rate (ORR), and secondary endpoints were overall survival, progression-free survival and duration of response. At a median follow-up of 31 weeks, the best response among patients with vaginal or vulvar cancer was stable disease. PD-L1 expression in ten patients was at least 1% and in three patients was less than 1%, while the other eleven patients were not tested. Nivolumab had a manageable safety profile [72].

## 24.14 Conclusion

Vaginal cancer is an extremely rare tumour, and unfortunately, there are not many clinical studies that are able to provide strong results and therapeutic options. Often, the same treatments as those used for cervical cancer are employed. The biology of the disease should lead to an individualized medical treatment wherever is possible. Usually, patients with vaginal cancer are elderly, and this significantly impacts the treatment they will receive. Using oncology counseling and multidisciplinary teams (MDTs) is a must for making better decisions for these patients. As a large proportion of vaginal cancer is HPV dependent, the impact is likely to be diminished in the future in developed countries due to the vaccination of young girls, comprising a great economic benefit to health systems.

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# Chapter 25

## Diagnosis and Management of Gestational Trophoblastic Neoplasia



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**Abstract** Gestational trophoblastic neoplasia (GTN) is the term used for an uncommon group of diseases that originate in the placenta and have the potential to locally invade the uterus and metastasize. The histological entities included in this group are: partial (PHM) and complete hydatidiform mole (CHM), invasive mole (IM), choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT).

**Keywords** Gestational Trophoblastic Neoplasia · Biomarkers · Gynecological cancer

### 25.1 Introduction

Gestational trophoblastic neoplasia (GTN) is the term used for an uncommon group of diseases that originate in the placenta and have the potential to locally invade the uterus and metastasize. The histological entities included in this group are: partial (PHM) and complete hydatidiform mole (CHM), invasive mole (IM), choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). With the exception of PSTT and ETT, all gestational trophoblastic tumors develop from the cyto- and syncytial cells of the villous trophoblast and produce abundant amounts of human chorionic gonadotropin (hCG), the measurement of which serves as a reliable tumor marker for diagnosis, monitoring treatment

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response and follow-up to detect recurrence. PSTT and ETT, on the other hand, are gestational trophoblastic tumors that originate from the intermediate cells of extravillous trophoblast and produce hCG sparsely, making its use as a tumor marker less reliable. Prior to the development of effective chemotherapy for GTN in 1956 [1], the majority of patients with disease localized to the uterus were cured with hysterectomy, whereas metastatic disease was almost uniformly fatal. Currently, most women with GTN can be cured and their reproductive function preserved providing they are managed according to well-established guidelines. GTN is an uncommon disease which ideally should be managed at trophoblastic disease centers where concentration of cases provides clinicians with ample experience, opportunities for research, and improved outcomes [2]. Since many patients will be managed locally, it is the purpose of this review to familiarize clinicians who encounter these patients with the latest advances in the field in order to optimize their patient's outcome.

## 25.2 Epidemiology

GTN arises most commonly after a molar pregnancy, but can also occur after normal or ectopic pregnancies and spontaneous or induced abortions. Approximately 50% of cases of GTN arise from molar pregnancy, 25% from miscarriages or tubal pregnancy, and 25% from term or preterm pregnancy. Non-metastatic disease develops in 10–15% of women with CHM and 1–5% of women following PHM. Metastatic disease which can be either metastatic mole or CCA occurs in 5% of patients with CHM and rarely after PHM [3]. GTN is 1000 times more likely to occur after CHM than after another type of pregnancy. There are wide regional variations in the incidence of CHM which range from 0.57–1.1 per 1000 pregnancies in North America, Europe, Australia and New Zealand to 2.0 per 1000 pregnancies in Southeast Asia and Japan [4–8]. There also appears to be an increased incidence in American Indians, Inuits, Hispanics and African Americans [9]. The risk factors for the development of CHM are advanced maternal age (>40), ethnicity, prior molar pregnancy, and decreased dietary beta-carotene and animal fat [10–13].

The incidence of GTN following non-molar pregnancies, usually CCA but rarely PSTT and ETT, in Europe and North America is estimated at approximately 1:40,000 pregnancies, whereas in Southeast Asia and Japan the incidence is higher at 9.2 and 3.3 per 40,000 pregnancies, respectively [14, 15]. The incidence of GTN after spontaneous miscarriage is estimated at 1:15,000 pregnancies, while the incidence after a term pregnancy is 1:150,000 pregnancies. The overall incidence of GTN following all types of pregnancies is estimated at 1:40,000 [16].

## 25.3 Pathology

CHM is characterized by clusters of hydropic villi with trophoblastic hyperplasia and atypia. CHM are diploid and have a chromosomal pattern of either 46XX or 46XY. All XX chromosomes are androgenetic, that is, from paternal origin and arise from fertilization of an empty ovum by a haploid sperm that then undergoes duplication. Occasionally, CHM arises from fertilization of an empty ovum by two sperm [17–19]. Maternal chromosomes are absent, although one can identify maternal mitochondrial DNA [20].

PHM shows a variable amount of abnormal villous development and focal trophoblastic hyperplasia in association with identifiable fetal or embryonic tissue. PHM contain both maternal and paternal chromosomes and are triploid, typically XXY, which occurs by fertilization of a normal ovum by two sperm [21–23].

IM occurs when molar tissue invades the myometrial wall. Deep myometrial invasion can lead to uterine rupture and severe intraperitoneal hemorrhage. Most IM remain localized to the uterus, but metastases to distant sites do occur [3].

CCA consists of invasive, highly vascular and anaplastic trophoblastic tissue including cytotrophoblasts and syncytiotrophoblasts without villi. CCA metastasizes hematogenously and can follow any type of pregnancy, but most commonly develops after CHM. The most common metastatic site is the lungs which are involved in over 80% of patients with metastases [3]. Vaginal metastases are noted in 30% of patients. Distant sites such as the liver, brain, kidney, gastrointestinal tract and spleen occur in about 10% of patients and constitute the highest risk of death. Widespread metastatic disease is more likely to be encountered after non-molar pregnancies where early diagnosis is frequently delayed [3].

PSTT are the malignant equivalent of extravillous, intermediate trophoblast. Microscopically these tumors show no chorionic villi and are characterized by a proliferation of cells with oval nuclei and abundant eosinophilic cytoplasm. They are seen more commonly after a non-molar abortion or term pregnancy, but can occur after a molar gestation as well. These tumors are slow growing and tend to locally infiltrate the myometrium at which point they can metastasize both via the hematologic and lymphatic systems [24, 25]. Endocrinologically they differ from either IM or CCA in that they secrete very low levels of hCG. PSTT are also characterized by higher levels of free *B*-hCG [26]. Therefore a large tumor burden may be present before the disease is diagnosed. These tumors tend to remain localized in the uterus for long periods before metastasizing to regional lymph nodes or other metastatic sites.

ETT is a variant of PSTT with similar clinical behavior and also derived from intermediate trophoblastic cells, but characteristically form tumor nodules which are characterized by increased hyalinization. In both of these tumors the hCG production is quite sparse [27, 28].



## 25.4 Clinical Presentation

GTN has a varied presentation depending upon the antecedent pregnancy, extent of disease and histopathology. Post-molar GTN (usually IM, occasionally CCA) most commonly presents following evacuation of a high-risk CHM characterized by pre-evacuation uterine size larger than dates, hCG levels >100,000 mIU/ml, and bilateral ovarian enlargement caused by excess hCG stimulation (i.e., theca lutein cysts) [29]. Clinical signs suggestive of persistent disease are enlarged uterus and irregular bleeding. Rarely a metastatic nodule will bleed causing vaginal hemorrhage or hemoptysis. Usually, however, pulmonary metastases are silent and are detected radiographically [3].

In contrast, most patients who develop GTN following a non-molar pregnancy present with widespread metastatic CCA which may involve the lungs, vagina, liver, kidneys, and brain [3]. Symptoms and signs vary with disease location. Patients with brain metastases present with seizures, headaches, or hemiparesis. Patients with pulmonary metastases can present with hemoptysis, shortness of breath, and/or pleuritic chest pain. It is usually diagnosed after the patient presents with signs and symptoms due to bleeding from a metastatic site [3].

## 25.5 Diagnosis

### 25.5.1 hCG Measurement

hCG measurement is key to effective management of GTN. hCG is synthesized primarily by syncytiotrophoblastic cells of the villous trophoblast. It is a glycoprotein which consists of an alpha-subunit common to other glycoproteins, and a beta-subunit which is hormone specific. Therefore, the measurement of hCG in patients with GTN should be performed by assays that measure the *B*-subunit only [30]. The levels and serial changes in *B*-hCG are essential to diagnose and track the treatment and outcome of GTN. After evacuation of a molar pregnancy, *B*-hCG levels usually disappear in 8–12 weeks [29]. Persistence of hCG levels indicate local or metastatic disease. With monitoring of the serum or urinary hCG levels, persistent disease can be detected early and therapy instituted. During treatment *B*-hCG tests should be performed weekly in the same laboratory for consistency. The *B*-hCG response to each course of treatment is used as a guide to determine whether to continue treatment with the same agent or switch to another.

False positive hCG tests, called phantom hCG, can occur due to the presence of heterophile antibodies that interfere with the immunoassay [30]. Although a rare occurrence, false positive hCG tests can be confusing to clinicians when attempting to diagnose disorders of pregnancy such as ectopic pregnancies and GTN. Misinterpretations of false positive tests have led to inappropriate treatment including surgery and chemotherapy based only on the persistently elevated serum

*B*-hCG levels. A false positive hCG result should be suspected if the clinical picture and the laboratory results are discordant, if there is no identifiable antecedent pregnancy, or if patients under treatment with persistent low levels do not respond appropriately. In rare instances, particularly in women approaching menopause, the source of the false positive hCG is the pituitary gland. When a false positive hCG test is suspected, a urinary assay should be performed since heterophile antibodies do not cross the renal tubules [30]. Pituitary hCG can be suppressed by the administration of birth control pills [31].

### **25.5.2 Following a Molar Pregnancy**

The diagnosis of post-molar GTN is based on the following International Federation of Gynecologists and Obstetricians (FIGO) guidelines [32]:

1. a plateau in *B*-hCG levels over at least 3 weeks,
2. a 10% or greater rise in *B*-hCG levels for three or more values over at least 2 weeks,
3. persistence of *B*-hCG levels 6 months after molar evacuation.
4. histologic evidence of choriocarcinoma.
5. presence of metastatic disease.

### **25.5.3 Following a Non-molar Pregnancy**

Patients who develop rising hCG values following a non-molar pregnancy have CCA until proven otherwise. Serum hCG levels are not routinely performed after non-molar pregnancies (except in following ectopics), unless the woman has had a previous molar pregnancy when it becomes the standard of care because of the increased risk of developing GTN. However, any woman in the reproductive age group who presents with abnormal bleeding or evidence of metastatic disease, should undergo hCG screening to rule out choriocarcinoma. At this point a thorough clinical and radiologic evaluation of the patient should be carried out to determine the extent of disease. Rapid growth, widespread dissemination and a high propensity for hemorrhage makes this tumor a medical emergency.

## **25.6 Staging and Risk Assessment**

Most patients who develop GTN after a molar pregnancy are detected early by hCG monitoring, so detailed investigation is rarely needed. Once it is determined that a patient has an elevated and rising hCG level, pelvic ultrasonography should be done

to confirm the absence of a normal pregnancy, to measure the uterine size and volume, to determine spread of disease within the pelvis and evidence of retained tumor or invasion [33]. Since pulmonary metastases are common, chest radiography is essential. Chest CT scan is not needed when a chest x-ray is normal since discovery of micrometastases seen in 40% of patients does not affect outcome [34]. However, if lesions are noted on chest x-ray, brain MRI and chest/abdominal/pelvic CT scans are recommended to exclude widespread disease which would affect management. If the brain MRI is equivocal a lumbar puncture to measure the cerebrospinal fluid/plasma hCG ratio (normal <1:60) can be used to confirm or exclude cerebral involvement [35, 36]. Blood tests to assess renal and hepatic function, peripheral blood counts, and baseline serum hCG levels should be obtained before chemotherapy is started. A speculum examination should be performed to identify the presence of vaginal metastases which may cause sudden heavy vaginal bleeding. It is usually not necessary to obtain histologic confirmation of the diagnosis because of the highly vascular nature of the tumor and the risk of hemorrhage. However, all available pathology should be reviewed. PET scanning with [18] F-fluorodeoxyglucose is sometimes indicated to identify sites of active disease, and confirm sites of active disease found on conventional imaging particularly when contemplating surgical removal [37].

In 2002 the FIGO Cancer Committee recommended that all physicians treating patients with GTN use an anatomical staging and prognostic scoring system to allow for comparison of data and guide the selection of the appropriate regimen for treatment (Tables 25.1 and 25.2) [38, 39]. Patients with PSTT and ETT are staged separately. The prognostic score effectively predicts the potential for the development of resistance to single agent chemotherapy with methotrexate and actinomycin D. A score of 0–6 suggests low-risk of resistance to monochemotherapy, whereas a score of >6 indicates a high-risk of resistance. Patients with scores >6 have a low chance of being cured with single agents and need multidrug treatment. Cure rates of 100% in low-risk and 80–90% in high-risk cases can be achieved with appropriate management. Despite the success of chemotherapy, other modalities such as surgery and radiation therapy should also be utilized where indicated, particularly in the patients with high-risk scores [40].

**Table 25.1** FIGO anatomical staging of gestational trophoblastic neoplasia

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures
Stage III	GTN extends to the lungs, with or without genital tract involvement
Stage IV	All other metastatic sites

**Table 25.2** Modified WHO prognostic scoring system

Prognostic factors	Score			
	0	1	2	4
Age (yrs)	<40	>39	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval (months)	<4	>3, <7	>6, <13	>12
Pretreatment serum hCG (mIU/ml)	<10 <sup>3</sup>	10 <sup>3</sup> –<10 <sup>4</sup>	10 <sup>4</sup> –<10 <sup>5</sup>	10 <sup>5</sup>
Largest tumor, including uterine (cm)	–	3–<5	>4	
Site of metastases	Lung	Spleen Kidney	GI tract	Brain Liver
Number of metastases	–	1–4	5–8	>8
Prior failed chemotherapy drugs	–	–	Single	Two drug

## 25.7 Management of Low-Risk GTN

Approximately 95% of patients with post-molar GTN have low-risk scores (0–6) and can anticipate a complete cure usually with single agents with preservation of reproductive function, if desired. Patients with stage I (non-metastatic) GTN who desire sterilization can opt for hysterectomy, although chemotherapy should still be administered to prevent persistent active disease due to occult metastases. A second D&C does not appear to have substantial therapeutic value, but may be necessary if the patient develops heavy bleeding due to retained products of conception [41, 42].

For most low-risk patients, monotherapy with methotrexate (MTX) or actinomycin D (ActD) is the preferred treatment [43]. A number of different regimens are currently in use which have been reported to achieve 50–90% remissions (Table 25.3) [32, 43]. The wide variability results from differences in dose, frequency, route of administration, and patient selection [43, 44]. MTX with folinic acid (also called calcium leucovorin) rescue (MTXFA) is the initial choice at the New England Trophoblastic Disease Center because it is effective, well tolerated, convenient for the patient, and cost effective. There is no hair loss and only about 5% of patients experience mouth ulcers, sore eyes, or rarely pleuritic or peritoneal pains from serositis [45]. ActD should be substituted for MTX if there is evidence of abnormal liver function tests. Courses are repeated every 2 weeks until the hCG level becomes undetectable. Patients with low-risk disease should receive three courses after remission is achieved to eliminate any residual tumor and reduce the chance of relapse [46]. Patients who develop resistance to MTXFA as determined by an inadequate response, plateau, or re-elevation of the hCG level, should be switched to ActD or multidrug therapy. The multidrug regimen we recommend for patients resistant to monotherapy consists of MTX, ActD, etoposide, cyclophosphamide and Vincristin (EMACO) (Table 25.4) [3]. Because survival in patients with low-risk disease is 100%, the least toxic regimens should always be employed initially. Only 30% of patients with a WHO score of 5–6 can be cured with monotherapy and should receive multidrug regimens initially. Characteristically these patients have hCG levels >100,000 mIU/ml and doppler ultrasound evidence of large tumor

**Table 25.3** Single-agent regimens for low-risk gestational trophoblastic neoplasms

MTX regimens		Primary remission
<b>Rates (%) [100]</b>		
1	MTX: 0.4–0.5 mg/kg IV or IM daily for 5 days	87–93
2	MTX: 30–50 mg/m <sup>2</sup> IM weekly	49–74
3	MTX-FA	74–90
	MTX 1 mg/kg IM or IV on days 1,3,5,7	
	FA 15 mg PO days 2,4,6,8	
4	High dose IV MTX/FA	69–90
	MTX 100 mg/m <sup>2</sup> IV bolus	
	MTX 200 mg/m <sup>2</sup> 12 h infusion	
	FA 15 mg q 12 h in 4 doses IM or PO beginning 24 h after starting MTX.	
<b>Actinomycin D regimens</b> (Vesicant-If administered peripherally, give through free flowing IV)		
ActD 10–12 mcg/kg IV push daily for 5 days		77–94
Act D 1.25 mg/m <sup>2</sup> IV push q 2 wks		69–90
<b>Sequential chemotherapy</b>		<b>100</b>

MTX methotrexate, ActD actinomycin D, FA folic acid (a.k.a. calcium leucovorin)  
 IV intravenous, IM intramuscular, PO by mouth

**Table 25.4** EMA/CO regimen

Day	Drug	Dose
1	Etoposide	100 mg/m <sup>2</sup> by infusion in 200 ml
		NS over 30 min
	ActD	0.5 mg IVP
	MTX	100 mg/m <sup>2</sup> IVP
200 mg/m <sup>2</sup> by infusion over 12 h		
2	Etoposide	100 mg/m <sup>2</sup> by infusion in 200 ml
		NS over 30 min
	ActD	0.5 mg IVP
	Folinic acid	15 mg q 12 h × 4 doses IM or PO beginning 24 h after starting MTX
8	Cyclophosphamide	600 mg/m <sup>2</sup> by infusion in NS over 30 min
	Vincristine	1 mg/m <sup>2</sup> IVP

EMA/CO, etoposide, actinomycin D, methotrexate, cyclophosphamide, vincristine  
 FA folic acid, actD actinomycin (Cosmegen<sup>R</sup>), MTX methotrexate, IVP intravenous push, IM intramuscular, PO by mouth, NS normal saline

burden [47]. Remission is achieved when the hCG level becomes undetectable for three consecutive weeks. At this point the patient should be followed with monthly hCG levels for 12 months to detect relapse before becoming pregnant. During this time effective contraception is mandatory. The use of birth control pills has been shown to be safe [29]. However, we do not recommend insertion of intrauterine

devices until the hCG level becomes undetectable because of the risk of uterine perforation, bleeding and infection if residual tumor is present. Pregnancy may be undertaken after 1 year of normal hCG values.

## 25.8 Management of PSTT and ETT

The primary treatment of patients with PSTT and ETT is surgical because of their relative resistance to chemotherapy. Lymph node sampling is recommended at the time of hysterectomy if there is evidence of deep myometrial invasion. Cures have been reported in patients with metastatic disease with a multidrug regimen consisting of etoposide, methotrexate, actinomycin D, and cisplatin (EMA/EP) particularly when the time interval from the antecedent pregnancy is <4 years. (Table 25.6) [48–52]. Although not generally applicable, the efficacy of fertility-sparing surgery in select cases has been reported [53, 54].

## 25.9 Management of High-Risk GTN

Patients with FIGO stage IV and stages II-III whose scores are >6 are at high risk of developing drug resistance and should be treated initially with multiagent regimens. EMACO (Table 25.4), which consists of etoposide, MTX, ActD, Cytosin and Oncovin, is the most widely used initial regimen for high-risk GTN since it is effective with cure rates ranging from 70–90%, and has predictable and easily managed short-term toxic effects [55–59]. A similar regimen, EMA/EP (Table 25.5),

**Table 25.5** EP/EMA regimen

Day	Drug	Dose
1	Etoposide	100 mg/m <sup>2</sup> by infusion in 200 ml
		NS over 30 min
	ActD	0.5 mg IVP
	MTX	100 mg/m <sup>2</sup> IVP
		200 mg/m <sup>2</sup> by infusion over 12 h
2	Etoposide	100 mg/m <sup>2</sup> by infusion in 200 ml
		NS over 30 min
	ActD	0.5 mg IVP
8	Cisplatin	75 mg/m <sup>2</sup> IV with prehydration
	Etoposide	100 mg/m <sup>2</sup> by infusion in 200 ml
		NS over 30 m

EP/EMA, etoposide, methotrexate, actinomycin D, cisplatin

FA folic acid, actD actinomycin (Cosmegen<sup>®</sup>), MTX methotrexate, IVP intravenous push, IM intramuscular, PO by mouth, NS normal saline

substituting cisplatin for Oncovin and Cytosan, can be utilized as salvage therapy when resistance to EMACO occurs [60, 61]. Treatment should be dose-intensive every 2–3 weeks, toxicity permitting. Alopecia is universal as is myelosuppression, although the use of recombinant hematopoietic growth factors such as Granulocyte Colony Stimulating Factor (G-CSF) and, when absolutely necessary, platelet transfusions allow for continued treatment intensity and avoidance of neutropenic febrile episodes. Treatment should be continued until the hCG level becomes undetectable and remains undetectable for three consecutive weeks. Three to four courses of consolidation therapy is strongly recommended because the relapse rate in patients with high-risk disease can approach 10% [62, 63]. Seckl and co-authors have reported that the cumulative 5-year survival rate of patients with high-risk disease treated with EMACO is between 75% and 90%. Long-term survival was only 27% when liver metastases were present, 70% with brain metastases, and 10% with involvement of both sites. Deaths occurred in patients who presented with widespread disease frequently due to delayed diagnosis, from life-threatening complications such as respiratory failure and central nervous system hemorrhage, from the development of drug resistance, or from inadequate treatment [64]. The Charing Cross group has utilized induction low-dose etoposide 100 mg/m<sup>2</sup> and cisplatin 20 mg/m<sup>2</sup> (days 1 and 2 every 7 days) in selected patients with high tumor burden to almost completely eliminate early mortality which may result from respiratory compromise and hemorrhage [65].

The use of radiation therapy in patients with GTN is limited to the treatment of brain metastases where whole head or localized radiation therapy in conjunction with chemotherapy can prevent a life-threatening or debilitating hemorrhage and should be initiated promptly [65]. Solitary superficial cerebral lesions are best treated surgically [66].

Surgery should also be considered as an important adjunct in the management of high risk patients [67]. Hysterectomy in patients with heavy bleeding, large bulky intrauterine disease, or in the presence of significant pelvic sepsis should be performed regardless of the patient's parity. Removal of tumor masses in the bowel should also be performed because of the risk of hemorrhage. Unresponsive masses in the liver and kidneys should be removed, although embolization has been used with some success in controlling liver metastases. Splenectomy should always be performed when that organ is involved. After completion of chemotherapy, patients with high-risk disease should be followed for 12–24 months before pregnancy is attempted.

Although late sequelae from chemotherapy are very rare, an increase incidence of risk of another cancer, most commonly leukemia, has been reported in association with etoposide making long-term surveillance in these patients warranted [68]. Recent data from the same institution indicates lower second cancer rates than previously reported, although patients may experience earlier menopause [69].

## 25.10 Management of Recurrent/Resistant Disease

Chemoresistant or recurrent disease, usually encountered in patients with high-risk disease, poses a significant treatment challenge [32]. This group is characterized by multi-organ involvement. When resistance or relapse occurs, re-imaging should be performed to determine the feasibility of surgery. PET scanning can help to identify the site of active disease [37]. The half-life for hCG is 48 h or less after surgery if the disease has been completely removed. However, when surgery or radiation is not possible or successful, several salvage regimens can be utilized. Table 25.6 contains

**Table 25.6** Salvage regimens for recurrent or resistant GTN

<b>BEP protocol for resistant high-risk GTN</b>	
Days 1–5	Etoposide (VP-16), 100 mg/m <sup>2</sup> , IVB in 500 ml NS over 1 h. Cisplatin, 20 mg/m <sup>2</sup> , IVB in 250 ml NS over w2 h.
Weekly	Bleomycin, 30 units, IVCI in 1 L NS over 6–12 h

Repeat cycles every 21 days × 4

Monitor for bleomycin toxicity with pulmonary function tests; maximum bleomycin dose, 270 units

Administer pegfilgrastim 6 mg SQ day 8 or filgrastim 300 ug SQ days 6–14

NS normal saline, IVB intravenous bolus, IVCI intravenous continuous infusion

<b>ICE protocol for resistant high-risk GTN<sup>a</sup></b>	
Day 1	CARBOPLATIN, AUC 6 <sup>a</sup> , IV bolus, infuse over 30–60 min.
Days 1,2,3	MESNA, 300 mg/m <sup>2</sup> , IV bolus, infuse over 15 min before Ifosphamide and repeat at 3 and 6 h after start of Ifosphamide. The last dose may be given PO.
	IFOSFAMIDE, 1500 mg/m <sup>2</sup> , IVBolus, Infuse over 30–60 min.
	ETOPOSIDE, 100 mg/m <sup>2</sup> , IV CI, infuse over 1 h after Ifosphamide.

Administer pegfilgrastim 6 mg SQ day 4 or filgrastim 300 µg SQ days 6–14

IVB intravenous bolus, IVCI intravenous continuous infusion

<sup>a</sup>Adjust as needed for extensive prior chemotherapy or specifics for patient condition

<b>TE/TP doublet for resistant high-risk GTN</b>		
Day 1	Paclitaxel	135 mg/m <sup>2</sup> , in 250 ml NS over 3 h
	Mannitol	10% in 500 ml NS over 1 h
	Cisplatin	60 mg/m <sup>2</sup> , in 1 L NS over 3 h
	Posthydration	1 L NS + KCL 20 mmol + 1 gm MgSO <sub>4</sub> over 2 h
Day 15	Paclitaxel	135 mg/m <sup>2</sup> , in 250 ml NS over 3 h
	Etoposide	150 mg/m <sup>2</sup> , in 1 L NS over 1 h

Repeat cycle q.28 days

Pegfilgrastim 6 mg the day after each dose

NS normal saline



a list of the various salvage regimens that have been utilized successfully in the management of resistant/recurrent GTN. Although anecdotal successes have been reported with high-dose chemotherapy with peripheral stem-cell transplantation, this technique does not appear to cure many patients with refractory disease [70, 71].

Although outcomes for more than 98% of women with GTN are excellent, a few women die from the disease because of late presentation and diagnosis and drug resistance. The best outcomes are achieved when patients are treated under the supervision of a multidisciplinary team.

## 25.11 Quiescent GTN

Some women with a history of GTN or non-molar pregnancy have a consistently low level of hCG (<200 mIU/ml) without detectable disease. The condition is characterized by an undetectable level of hyperglycosylated hCG (H-hCG), which is a marker for invasive trophoblastic disease [72]. Treatment with either chemotherapy or surgery is ineffective. The source of the hCG is presumably dormant though still viable syncytiotrophoblast cells in the absence of cytotrophoblast or intermediate trophoblast without invasive potential. Approximately 20–25% of patients with quiescent GTN go on to develop active GTN as reflected in rising hCG and H-hCG levels [73]. H-hCG may become detectable in serum weeks and months before there is a detectable rise in the hCG level or before there is clinical evidence of disease. Quiescent GTN patients should be closely monitored with periodic hCG testing and should avoid pregnancy until the condition is resolved [74]. Treatment is indicated only when the hCG level is rising and there is evidence of active disease [75, 76].

## 25.12 Subsequent Pregnancy

Patients with GTN treated successfully with chemotherapy can expect normal reproductive function [77–80]. The NETDC database has follow-up on 667 subsequent pregnancies in GTN patients treated between July 1, 1965 and December 31, 2013 that resulted in 446 term live births (66.9%), 44 premature deliveries (6.6%), 7 ectopic pregnancies (1.0%), 10 stillbirths (1.5%), and 10 repeat molar pregnancies (1.5%). First- and second-trimester spontaneous abortions occurred in 123 pregnancies (18.4%). There were 28 therapeutic abortions (4.2%). Major and minor congenital anomalies were detected in only 12 of 500 births (2.4%) [80]. These values are comparable to the general gestational population. The low incidence of congenital malformations is reassuring in spite of the fact that chemotherapeutic agents are known to have teratogenic and mutagenic potential.

A total of 3191 subsequent pregnancies from multiple centers have been reported which resulted in 71% full term deliveries, 4.7% premature births, 1.3% stillbirths and 14.3% spontaneous miscarriages. Despite the use of potentially teratogenic

drugs, no increase in congenital malformations have been reported [3]. Furthermore Woolas and colleagues noted that there was no difference in either the conception rate or pregnancy outcome in patients treated with single or multiple agent protocols. The fertility rate was essentially normal as well [81].

Although we advise patients to practice strict contraception during follow-up, patients occasionally become pregnant, either accidentally or intentionally, before their follow-up has been completed. Early pregnancy after undergoing chemotherapy for GTN can delay diagnosis of disease recurrence, as most recurrences occur between 3 and 6 months after completing treatment [39, 40, 63]. When this occurs and the pregnancy is desired, we monitor the developing fetus and placenta with sonograms at 6 and 10 weeks of gestation. If the 10 week sonogram appears normal there is little likelihood of recurrence [82, 83]. Furthermore, pregnancies occurring before hCG follow-up is complete have no increased risk of abnormalities. We strongly advise these patients to undergo hCG testing at the 6 week post-partum or post-abort check-up to ensure complete remission.

## 25.13 Psychosocial Issues

Women who develop GTN may experience significant mood disturbance, marital and sexual problems, and concerns over future fertility [84]. Because GTN is a consequence of pregnancy, patients and their partners must confront the loss of a pregnancy at the same time they face concerns regarding malignancy. Patients can experience clinically significant levels of anxiety, fatigue, anger, confusion, sexual problems and concern for future pregnancy that last for protracted periods of time. Patients with metastatic disease are particularly at risk for psychological disturbances and need assessments and interventions both during treatment and after remission is attained [85].

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# Chapter 26

## Prostate Cancer



Helena Luna Pais, João Ulrich, and Leonor Ribeiro

**Abstract** Prostate cancer (PC a) is the second most common cancer worldwide in males. The incidence increases with age and positive family history. Most cancers are adenocarcinomas (>95%), multifocal and originated in the peripheral zone of prostate. Localized PCa is typically asymptomatic and is discovered through a rise in serum PSA or, less commonly, a suspicious digital rectum examination. Hesitance, urgency, poor urine stream, nocturia and incomplete bladder emptying are the most frequently reported symptoms. Their presence suggests advanced disease. On the other hand, bone pain raises the suspicion of metastatic disease. Transrectal ultrasound guided biopsy is the standard method of diagnosis. Treatment strategy is driven by tumor staging and can include a wide variety of approaches such as active surveillance, surgery, radiotherapy and/or medical therapy. Recently, there was the development of multiple new active treatment modalities, particularly in the setting of advanced disease.

**Keywords** Prostate cancer · Diagnosis · Treatment · Prognosis · Localized disease · Metastatic castration-sensitive · Metastatic castration resistant

### 26.1 Introduction

The term *prostate* is originally derived from the Greek *prostates*, which means “one who stands before” and was first used by Herophilus of Alexandria in 335 B.C. to describe seminal vesicles and epididymis (*prostatai adenoeides*). However its first use within a medical context to describe the prostate took place more than 2000 years afterwards, as the prostate was not discovered until then [1].

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Anatomically it is divided in a peripheral zone, a central cone-shaped zone and the apex, at the confluence of the ejaculatory ducts and the prostatic urethra. Lateral to the urethra there are two portions of glandular tissue called the transitional zone.

## 26.2 Epidemiology and Risk Factors for Prostate Cancer

Prostate Cancer (PCa) is the most frequent cancer in males in economically developed countries and the second most frequently diagnosed cancer in the world, accounting for 14% of all new cancer cases. It is also the sixth leading cause of death by cancer worldwide [2]. It is estimated that PCa will continually rise worldwide approximately by 3% a year [3].

Since the availability of Prostate Cancer Antigen (PSA) measurement, PCa epidemiology has changed a lot. In fact prostate cancer incidence and mortality are greatly variable worldwide with 2–5 times higher rates in developed countries [2, 4] which is in part attributable to increased detection capability with widespread PSA testing of asymptomatic individuals and transrectal ultrasound (TRUS) in these regions.

PSA screening is the single most important risk factor for PCa diagnosis, [5] with a relevant increase in asymptomatic PCa diagnosis and a concurrent decrease in the prevalence of latent prostate cancer in autopsy studies from pre to post PSA era [6].

The risk of PCa increases with age, with both incidence and mortality higher in men over 70 years of age, and 97% of PCa cases occurring in men over 50 years old [7]. In fact, while the probability of developing prostate cancer is 0,005% for men younger than 39 years of age, it is 2,2% for men aged 40–59 years old and 13,7% for those aged 60–79 years old [8].

Ethnicity is also an irrefutable risk factor for PCa with higher incidence, younger age and more advanced anatomic stage at diagnosis and higher mortality rates reported in black men comparing to white men [9]. On the other hand PCa rates in Asia are among the lowest in the world, although there has been an increase in most of the countries [10].

Family history also plays a role as men with first-degree family history of PCa have a rate ratio of 2.48 [95% confidence interval, 2.25–2.74] of developing PCa, that increases with an increasing number of affected family members. In fact almost 60% of the prostate cancer incidence among men with first-degree family history is attributable to this risk factor [11].

Genetic characteristics have an important impact in these differences. BRCA 1 and 2 mutations are associated with poorer survival outcomes in men with PCa, as they confer a more aggressive phenotype with higher probability of nodal involvement and distant metastasis [12]. Patients carrying mutated DNA mismatch repair genes (Lynch Syndrome) are also at increased risk of PCa although PCa presence alone does not increase suspicion of Lynch Syndrome [13].



Several environmental risk and protective factors have been inconsistently reported with trends suggesting higher risk of PCa with consumption of carbohydrates, saturated and  $\omega$ -6 fats and certain vitamin supplements (vitamin A and folate) [14]. On the other hand consumption of plant phytochemicals such as lycopene, phenolic compounds (such as those found in coffee), fiber and  $\omega$ -3 fatty acids seem to decrease the risk and slow the progression of the disease [14].

Lifestyle factors like physical activity, and medication such as statins and non-steroid anti-inflammatory drugs have been reported do decrease the risk of PCa [14], while obesity seems to have a positive association with PCa [15]. High ejaculatory frequency seems to be protective [16]. Yet number of sexual partners and history of sexually transmitted infections might be deleterious [17].

### 26.3 Pathogenesis

Adenocarcinoma accounts for 95% of PCa cases, although some men develop other histological types such as small-cell neuroendocrine, adenoid cystic and basal cell (basaloid), squamous cell, urothelial, and sarcomatoid carcinomas. Even more rare histological types comprise primary prostate sarcomas, germ cell tumors, rhabdoid tumors, phyllodes tumors, malignant peripheral nerve sheath tumors, nephroblastoma, primary malignant melanoma, and Wilms' tumor, as well as primary hematopoietic malignancies [18].

Similar to other cancers, PCa results of the accumulation of genetic alterations in a cell originating malignant growth. However, there is a heterogeneous pattern of oncogene activation. Several gene alterations have been identified as relevant in the development or progression of sporadic PCa, such as gene mutations, hypermethylation, inactivation, aneuploidy, loss of heterozygosity of specific oncosuppressor genes (for example GSTp1, PTEN, Rb and p27) [19]. The activation of oncogenes is also important in PCa (such as the amplification of MYC and increased expression of BCL2) and, combined with p53 and Androgen Receptor (AR) mutation plays a special role in cancer progression and metastasis [19, 20].

Prostate adenocarcinomas originate from acinar and proximal duct epithelium, typically in the peripheral zones of the prostate and are associated with high-grade prostatic intraepithelial neoplasia (HGPIN) – the only recognized premalignant prostate lesion [21]. High grade carcinomas are frequently associated with HGPIN. Yet, low grade carcinomas are not, especially those that develop in the transition zone [18].

Although not considered a premalignant lesion, the presence of Atypical Small Acinar Proliferation (ASAP) is a significant predictor of subsequent carcinoma on repeated biopsy, as it refers to the presence of small atypical glands that display some features of carcinoma, yet not enough to render the diagnosis. In fact, up to 60% of ASAP on repeated needle biopsy confirm the presence of carcinoma [21].

## 26.4 Presentation and Diagnosis

Before the widespread use of PSA PCa was diagnosed only when symptoms were present. With the advent of screening with PSA and Digital Rectal Examination (DRE) PCa is rarely symptomatic at diagnosis. Symptoms resulting from bladder outlet obstruction are among the most common ones and usually occur only in advanced stages as they tend to reflect prostate enlargement or invasion of the peri-prostatic tissues. There are two types of bladder outlet obstruction symptoms: voiding symptoms (hesitancy, intermittency, incomplete emptying and a diminished urinary stream) and storage symptoms (frequency, nocturia, urgency and urge incontinence). Hematuria might also occur. None of these symptoms is specific of PCa and might also be present in other diseases such as Prostatic Benign Hyperplasia (PBH) [22]. Although even less frequently PCa might also present with symptoms secondary to metastatic disease such as skeletal related events (for instance bone pain, bone fracture and hypercalcemia).

### 26.4.1 Screening

Screening of asymptomatic men with PSA has been for years accepted in most European countries and in the US. It is nevertheless a controversial subject.

PSA is an enzyme produced mainly in prostatic epithelial cells that liquefies the ejaculate being mainly released into the semen but also leaking into circulation in small amounts. It is thus produced by prostatic cells, both benign and malignant and its serum concentration increases in prostatic manipulation (biopsy) but also in the hyperplastic and neoplastic prostate. In PCa the secretion to prostatic ducts decreases due to derangement of architecture and polarization of the epithelial cells leading to loss of normal secretory pathways hence increasing the amount of circulating PSA about 30-fold in comparison to normal epithelium and ten fold comparing to BPH [23, 24].

Serum PSA was first approved by the FDA in 1986 to monitor cancer progression and later in 1994 for cancer screening of asymptomatic man alongside DRE. The cutoff value of 3,0  $\mu\text{g/L}$  was considered the threshold above which prostate biopsy was recommended with positive predictive value for PCa of 25% (for World Health Organization-calibrated assays and 4,0  $\mu\text{g/l}$  in traditionally calibrated assays, to achieve the same sensitivity and specificity), although PCa might be present with lower PSA values. The normal range of PSA rises with age as result of gland enlargement and this should be taken into account [25].

The widespread use of PSA screening during the following decades greatly influenced PCa epidemiology, undoubtedly decreasing the frequency of advanced disease and disease specific mortality [26]. However it also increased the overdiagnosis or diagnosis of cases that, if left untreated would have not become clinically manifest over a patient's lifetime or result in cancer-related death; the rate of overdiagnosis

by PSA screening is still unknown ranging from 1,7% to 67% in different studies [27]. Overdiagnosis leads to overtreatment, which means a potential lack of benefit as well as unnecessary harm and cost from treatment of an overdiagnosed case [27]. This recent evidence generated controversy in PCa screening.

In order to evaluate the efficacy of PCa screening, two large randomized trials have been published: the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the United States and the European Randomized Study of Screening for Prostate Cancer (ERSPCa) in Europe and based on the results most of the major urologic societies have recommended against widespread mass screening for PCa at present, favoring opportunistic screening offered to men that know and accept the potential risks instead [25].

When an elevated PSA value is obtained, the most common explanation is the presence of BPH, although there are other causes such as prostatic inflammation/infection and perineal trauma. Therefore PSA measurement should generally be repeated a few weeks later, before additional studies are performed. If a consistent increase in PSA value is detected or a high baseline value is obtained (>20 ng/mL) further examination is recommended.

Other strategies to improve PSA diagnostic performance, namely PSA ratios and dynamic PSA calculations, are useful in the diagnosis and assessment of tumor aggressiveness. The percentage of free PSA (f/t PSA) and PSA density (PSA/prostate volume) are examples of calculated ratios. The percentage of free PSA (free/total PSA) has been used to improve cancer detection sensitivity when total PSA ranges between 1–4 ng/mL with a suggested cut-off at 20% for higher likelihood of cancer diagnosis (92% sensitivity and 23% specificity) [28]. PSA density (PSA per unit volume of prostate) >0.15 ng/mL/cc is suggestive of prostate cancer (when opposed to BPH) and used by some as a cut-off for biopsy [29]. Other emerging tests such as ACT-complexed PSA (cPSA) and the [–2] proPSA to free PSA ratio are still being assessed in clinical studies. PSA velocity (rate of PSA change over time in nanograms per milliliter per year) and PSA doubling time (number of months for a certain level of PSA to increase by a factor of two) are examples of PSA dynamic tests [30]. A PSA velocity cut-off of 0.75 ng/mL per year may provide information regarding the distinction of those with or without PCa [31]. PSA doubling time assessment is mainly used in the pre-treatment or post-treatment setting to predict aggressiveness [30].

### ***26.4.2 Diagnosis and Staging***

Besides serum PSA measurement, the main diagnostic tools for PCa are physical examination including DRE, and TRUS guided biopsy.

DRE provides information about the location, size and extend of the lesion (usually detected as a hard induration or nodularity) increasing the suspicion of cancer. Therefore it can be used for screening or further evaluation after an elevated PSA result. Presence of node spreading or skeletal involvement must also be accessed by

inguinal node evaluation, palpation of the skeleton looking for tender spots and neurological examination looking for spinal cord compression.

PCa study should include:

1. Routine studies: complete blood count (CBC), renal and liver function tests, calcium, alkaline phosphatase, urinalysis.
2. PSA (previously discussed)
3. Biopsy techniques. PCa diagnosis is given by histological examination [25]. Unlike PSA or DRE, TRUS is not used for screening but only for evaluation after a suspicion DRE or elevated PSA. The first elevated PSA level does not require an immediate biopsy and should instead be verified after a few weeks by the same assay. This, however, does not apply to high PSA values (>20 ng/ml) in which TRUS and biopsy are recommended, after prostatitis has been excluded [25].

PCa usually has a hypoechoic appearance in TRUS and a glandular volume of 30–40 mL should prompt the acquisition of 10–12 core samples, under antibiotic prophylaxis with quinolones, more frequently ciprofloxacin (oral or intravenous).

### 26.4.3 Gleason Score

The histologic sampling is usually graded using the Gleason Score, which is a grading system that classifies PCa according to the architectural pattern of the tumor, attributing a grade that is defined as the sum of the two most common grade patterns observed. It ranges from 2 (1+1), very well differentiated, to 10 (5+5), poorly differentiated. The change in tissue structure is good evidence for this differentiation [32]. However, nowadays the full Gleason spectrum is rarely used. In fact the attribution of Gleason scores from 2 to 5 is discouraged, as cancer with Gleason score less than 6 is rarely found in clinical practice [33]. There are significant deficiencies with the current application of the Gleason system that have had an impact on patient care. A Gleason score 7 can represent mostly well differentiated cancer with a lesser component of more poorly differentiated cancer (Gleason 3 + 4 = 7) or mostly poorly differentiated cancer with a smaller component of well differentiated cancer (4 + 3 = 7). Treatment decisions using a simplified single Gleason score of 7 fail to recognize that 3 + 4 = 7 and 4 + 3 = 7 are prognostically very different [129].

**Grade Groups** in 2013 a new grading system, based on data from Johns Hopkins Hospital, was proposed to address the confusion inherent in the Gleason system. A five-grade group system based on the much revised original Gleason score: grade group 1 (Gleason score < 6), grade group 2 (Gleason score 3 + 4 = 7), grade group 3 (Gleason score 4 + 3 = 7), grade group 4 (Gleason score 8), and grade group 5 (Gleason score 9–10) [129]. This new grading system and its terminology ‘Grade Groups 1–5’ were also adopted by the 2016 Edition of the World Health Organization of the Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs. For the foreseeable future to ease the transition to the new grading system,

it was agreed upon that both the Gleason grade and the Grade Groups would be included in pathology reports [130].

### 26.4.4 TNM Staging

The decision to further proceed with diagnostic or staging work-up depends on which treatment options are available to the patient, taking the patient's preference, age, and comorbidity into consideration [25].

TNM classification is used to stage PCa (Table 26.1). Local or T staging is based on DRE findings, TRUS or Magnetic Resonance Imaging (MRI). MRI is the best imaging exam to provide information about tumor size, prostate capsule integrity, extraprostatic invasion and seminal vesicle invasion. Further information is provided by the number and sites of positive prostate biopsies, the tumor grade, and the

**Table 26.1** TNM staging system for prostate adenocarcinoma.

<b>Primary tumor</b>	
Tx	Cannot access primary tumor
T0	No evidence of primary tumor
T1	Clinically inapparent tumor
T1a	Incidental histologic finding in $\leq 5\%$ of tissue resected
T1b	Incidental histologic finding in $> 5\%$ of tissue resected
T1c	Tumor identified in needle biopsy (elevated PSA level)
T2	Organ confined
T2a	Unilateral, involving one-half of 1 lobe or less
T2b	Unilateral involving more than one-half of 1 lobe
T2c	Bilateral disease
T3	Extraprostatic extension (unilateral/bilateral)
T3a	Extraprostatic extension/microscopic invasion of bladder neck
T3b	Seminal vesicle invasion
T4	Invasion of the bladder or rectum
<b>Lymph node</b>	
Nx	Regional lymph nodes not assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or more lymph nodes
<b>Distant metastasis</b>	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph nodes
M1b	Bone
M1c	Other sites with or without bone disease or more than one site of metastasis present

Adapted from the American Joint Committee on Cancer (AJCC) 8th Edition

**Table 26.2** Prostate cancer prognostic stage groups

T	N	M	PSA	Grade Group	Stage group
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a	N0	M0	≥10<20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	≥20	4	IIC
T1-2	N0	M0	≥20	1–4	IIIA
T3-4	N0	M0	Any	1–4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

Adapted from the American Joint Committee on Cancer (AJCC) 8th Edition

level of serum PSA. CT scan can also be used for local staging although it provides less information than MRI.

Lymph node status or N staging should only be assessed when curative treatment is planned as preoperative imaging has significant limitations in detection of small metastases (TRUS, CT and MRI are limited in detecting lymph node metastases <5 mm) and pelvic node dissection is the only reliable staging method for assessment of lymph nodes [25]. Patients with stage ≤T2, PSA <20 ng/ml, a Gleason score ≤6, and <50% positive biopsy cores have a <10% likelihood of having node metastases and can be spared nodal evaluation.

PCa metastases are most likely located in the bone. As such, M staging is best assessed by Bone Scintigraphy. Metastization is more frequent and bone scan is therefore recommended in symptomatic patients, if the serum PSA level is above 20 ng/mL or in the presence of undifferentiated tumor. PET Scan could be of value in equivocal cases, especially to differentiate active metastases from healing bones [25] (Table 26.2).

## 26.5 Treatment

This section will focus on the treatment of prostate adenocarcinoma. There is a great diversity of options in PCa treatment which have not always been clearly compared in clinical trials, especially for localized disease.

The adoption of a specific treatment along with its toxicity and morbidity depends on the risk level established by the life time expectancy, symptoms and tumor biology characteristics (such as Gleason score and PSA). Actively informing patients of advantages, pitfalls and relative contraindications of each treatment modality is therefore fundamental for a balanced intervention [34].

The approach used in this chapter is consistent with the National Comprehensive Cancer Network (NCCN) guidelines for the use of specific treatment modalities according to risk strategies based on several clinical variables.

At a first glance, the treatment for prostate cancer (PCa) can be directed to localized disease or metastatic disease.

## 26.6 Localized Prostate Cancer

### 26.6.1 *Stratifying Risk and Treatment Options for PCa*

Currently, practitioners have a limited set of tools to determine the risk/aggressiveness of localized PCa. The majority of risk stratification models used in clinical practice are based on [35, 142]:

- PSA values,
- Histologic Grade group (GG),
- TNM staging
- Extension and number of biopsy cores involved

The variety of models can be presented as normograms, simple or complex formulas or fixed values in guidelines. We will use the current NCCN risk stratification system presented in Table 26.3. Table 26.4 compares NCCN stratification system to others [35].

#### 26.6.1.1 Very Low-Risk and Low-Risk Patient Strategy

Active surveillance is the preferred strategy for men with very low risk and life expectancy  $\geq 20$  y and for men with low risk and life expectancy  $\geq 10$  y. Those who are not able to cope with the surveillance program due to anxiety or non-compliance should preferably be treated with local treatment options.

Local treatment options as radical prostatectomy or radiotherapy (such as external beam therapy [EBRT], low-dose-rate brachytherapy [LDR-BT] or high-dose-rate brachytherapy [HDR-BT]) are recommended [3, 4].

The ESMO 2015 guidelines [143] consider surgery and EBRT techniques (CRT and IMRT) as equal options for localized PCa, however underline the lack of large RCTs comparing contemporary techniques of different treatment modalities on quality of life or long-term survival in patients with low-risk [5]. Non-randomized studies have shown superiority of radical prostatectomy over RT or brachytherapy in overall survival, although not demonstrating statistically significant differences in cancer-related mortality [6]. Selection bias and confounding variables in long-term analysis might have influenced overall survival results [7].

**Table 26.3** NCCN pre-treatment PCa risk group stratification system

Risk Group	Very low	Low	Intermediate	High	Very high (locally advanced)	Metastatic	
						Regional lymph node	Distant metastasis
<b>Criteria</b>	T1c + GG 1 + Fewer than three prostate biopsy positive cores; ≤ 50% cancer in each core + PSA density <0.15 ng/mL/g	T1–T2a + GG 1 + PSA < 10 ng/mL	Intermediate risk factors (IRF): T2b–T2c GG = 2 or 3 PSA 10–20 ng/mL  Favorable: 1 IRF + GG 1 or 2 + <50% biopsy cores positive  Unfavorable: 2 or 3 IRF +/or GG 3 +/or >= 50% biopsy cores positive	T3a or GG 4 or 5 or PSA > 20 ng/mL	T3b–T4 or Primary Gleason pattern 5 or >4 cores with GG 4 or 5	Any T, N1 M0 Any GS Any PSA	Any T, any N, M1 Any GS Any PSA



**Table 26.4** Comparison between risk group stratifications for PCa

Institution/ organization	Low risk	Intermediate risk	High risk
<b>Harvard (D'Amico) EAU</b>	T1–T2a and GS $\leq 6$ and PSA $\leq 10$	T2b and/or GS = 7 and/or PSA >10–20 not low-risk	$\geq$ T2c or PSA > 20 or GS 8–10
<b>AUA</b>	T1–T2a and GG 1 and PSA < 10*	T2b–T2c or GG 2 or 3 or PSA 10–20 Favorable: GG 1 (with PSA 10–<20) OR GG 2 (with PSA<10) Unfavorable: GG 2 (with either PSA 10–<20 or clinical stage T2b–c) OR GG 3 (with PSA < 20)	$\geq$ T3 or PSA $\geq 20$ or GG 4 or 5
<b>ESMO</b>	T1–T2a and GS $\leq 6$ and PSA < 10	T2b and/or GS7 and/or PSA 10–20	$\geq$ T2c or GS 8–10 or PSA > 20

*AUA* American Urological Association, *EAU* European Association of Urology, *ESMO* European Society of medical oncology

\*if <34% of biopsy cores positive AND no core with >50% involved, AND PSA density <0.15 ng/ml/cc is considered very low risk

### 26.6.1.2 Favorable Intermediate-Risk Patient Strategy

Men with life expectancy  $\geq 10$  y should undergo radical prostatectomy (with Pelvic Lymph Node Dissection [PLND] in patients with risk of lymph node invasion > 2% as assessed by Cagiannos normogram) or opt for active surveillance. EBRT (including Whole Pelvic Radiotherapy [WPRT] if Roach formula for lymph nodes is superior to 15%) with or without Androgen Deprivation Therapy (ADT, 4–6 months) with or without complete/combined androgen blockade (CAB, which implies gonadotropin releasing hormone modulation with the addition of anti-androgen) is an option regardless of the life expectancy [3]. Brachytherapy in monotherapy can also be used in this setting.

### 26.6.1.3 Unfavorable Intermediate-Risk Patient Strategy

Radical prostatectomy (with Pelvic Lymph Node Dissection [PLND] in patients with risk of lymph node invasion > 2% as assessed by Cagiannos normogram) is still an option for men with life expectancy  $\geq 10$  y. EBRT with or without Androgen Deprivation Therapy with or without complete/combined androgen blockade is an option regardless of the life expectancy [3]. The addition of brachytherapy (BT) as boost is optional. Most physicians do not use brachytherapy in monotherapy given the risk of potential undertreatment due to unfavorable coverage at distant peripheral zones.

#### **26.6.1.4 High-Risk and Very High-Risk Patient Strategy**

Prostatectomy combined with PLND for patients without tumor fixation to adjacent organs can be used. Other options include EBRT with BT boost (for patient with clinical and anatomical condition for BT). For those receiving RT, ADT with complete androgen blockage should also be given (2–3 years).

### **26.7 Therapeutic Modalities**

#### **26.7.1 Active Surveillance**

This option is an attempt to overcome overdiagnosis and overtreatment of PCa. Active surveillance is defined as a tight schedule follow-up with active clinical evaluation and exams (PSA no more often than every 6 months unless clinically indicated; DRE no more often than every 12 months unless clinically indicated; repeat prostate biopsy no more often than every 12 months unless clinically indicated; and repeat mpMRI no more often than every 12 months unless clinically indicated) with the objective to intervene with potential curative intent if the cancer progresses. These follow up recommendations are not based on randomized clinical trial results and therefore need further evidence. Treatment is required when, upon repeated biopsies, PCa samples with Gleason score 4 or 5 are found or when a greater number or extension of cores are involved [36]. PSA kinetics (PSA doubling-time and PSA velocity) is not an ideal trigger for biopsy because it is not associated with clinical important reclassification of biopsy results (pathology progression), [41, 42] therefore it should not be used to replace annual surveillance biopsy. In asymptomatic patients with a low life expectancy (<10 years) only observation is recommended until symptoms develop or are eminent (PSA > 100 ng/ml). Subsequently, a palliative treatment is provided.

#### **26.7.2 Surgery**

Radical prostatectomy (RP) is a treatment option when cancer can be completely excised surgically and no surgical contraindications are present. High-volume centers have best outcomes [43].

Laparoscopic radical prostatectomy has been increasing when compared to classic approaches to minimize invasiveness and open surgery related complications [44]. Most studies at the moment (non-Randomized Clinical Trials) do detect slight improved surgical margins and perioperative outcomes favoring minimal invasive techniques when compared to open surgery [44, 45]. Outcomes regarding tumor control are not well assessed due to short follow-up of patients treated with robotic surgery [46].

During RP a PLND is performed when the probability of nodal metastasis is >2% according to the normogram created by Cagiannos et al. [47] In clinical practice, this normogram reveals that only low-risk and few patients with intermediate risk should not be submitted to PLND. An extended technique should be performed (excision of lymph nodes in the anterior portion of the external iliac vein, pelvic side wall, medial bladder wall, posterior floor of the pelvis, Cooper's ligament distally and proximal internal iliac artery), given that twice as much nodal metastasis will be found.

Traditionally, RP for high-risk prostate cancer has been discouraged but some authors consider that there is room for surgery in high-risk patients for providing better staging and removing micrometastatic lymph nodes through extended PLND [48].

The use of hormone therapy prior to surgery is discouraged in most guidelines. A systematic review by Kumar et al. found no improvement of overall survival (OR 1.11, 95% CI 0.67 to 1.85,  $p = 0.69$ ) [49]. However, sub-group analyses by disease risk were not performed.

### 26.7.3 Radiotherapy

#### 26.7.3.1 External Beam Radiation Therapy (EBRT)

EBRT is a radiation therapy technique in which the patient is treated with beams of external radiation that must cross through the body (skin and nearby organs) until they reach the desired target (i.e. prostate, seminal vesicles with or without the irradiation of regional lymph nodes) with the calculated dose and preserving adjacent organs at risk.

EBRT will require a certain fractionation schedule and the "splitting" of the dose by fields, i.e. "angles of entry" of the radiation beams in the body.

Radiotherapy departments have EBRT techniques based on computerized tomography (CT) simulation and devices emitting megavoltage photons that can be either used in three-dimensional conformal radiotherapy technique (3D-CRT) or intensity modulated radiation therapy (IMRT). CT-based simulation allows to better delineate volumes and to improve field settings, which contributes to optimize the preservation of adjacent organs at risk. A systematic review of the literature by Morris et al. reported that 3D-CRT decreases toxicity and improves therapeutic index when compared the conventional radiotherapy (non-CT-based) [50].

This technological achievement was the beginning of further evolution in the improvement of dose escalation specifically to the tumor with modulation of beams intensity and computerized inverse-planning optimization strategies, which culminated in the development of IMRT (3D-CRT refinement). Also, the optimization of safety/tolerance radiation margins, image guidance to improve reproducibility of treatment and preserve organs at risk and the standardization of delineation guidelines and dosimetry reports were other technological hallmarks that allowed dose escalation.

Prostate cancer is a dose-responsive tumor. Many trials reported better outcomes with dose escalation. One example is the study performed by Kuban et al. in which 301 patients with PCa staged from T1b to T3 were randomized to 70 Gy or to 78 Gy EBRT. Freedom from biochemical or clinical failure (FFF) was superior in the 78-Gy arm (78%) as compared with the 70-Gy arm (59%;  $p = 0.004$ ). In this study, patients with initial PSA  $>10$  ng/ml benefited even more (78% vs. 39%,  $p = 0.001$ ) [51].

IMRT is a 3D-CRT refinement in which the radiation intensity is further modulated through the creation of beamlets of different intensities and by allowing shaping in each beam through multileafs. Computerized inverse planning further optimizes field settings. Studies concerning IMRT use in PCa have shown that it was superior to 3D-CRT regarding rectum and bladder protection based on dosimetric studies and clinical data. Organ sparing was even more significant, namely for small bowel and colon, when WPRT was used [52].

Current evidence recommends IMRT with minimal prescription doses of 75.6–79.2 Gy to the prostate (including or not seminal vesicles) for low-risk PCa and doses up to 81 Gy for intermediate to high-risk patients [36, 37, 55].

Treatment protocols enforcing accuracy of treatment are a cornerstone. Image-guided radiotherapy (IGRT) (e.g. portal images, cone beam CT and fiducial markers) and physiological preparation (e.g. bowel and rectal deflation and bladder filling) are respectively important to reduce margins and risk of adjacent organ complication, as well as to reduce movements of the prostate gland, which the IMRT or 3D-CRT cannot predict.

A radiobiological feature of PCa is the low  $\alpha/\beta$  ratio (ratio that depicts survival behavior after a certain amount of radiation), which ranges between 1 and 4 with most studies considering 1.5 [56]. Cells with low alfa-beta are more resistant against small doses of radiation. This means that hypofractionation schemes (treatment in which total radiation dose is divided into larger doses and higher than conventional doses per fraction, thus reducing the overall days of treatment) are an appropriate option if technological feasible.

More recently, moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials, and their efficacy regarding local control has been non-inferior to conventionally fractionated IMRT. Toxicity was similar between moderately hypofractionated and conventional regimens. Hypofractionated radiotherapy using 60 Gy in 20 fractions or 70 Gy in 28 fractions is recommended as a new standard of care for external-beam radiotherapy of localized prostate cancer [144–146].

RTOG 0415 trial randomly assigned a total of 1115 men with low-risk prostate cancer 1:1 to Conventional radiotherapy (C-RT) (73.8 Gy in 41 fractions over 8.2 weeks) or to hypofractionated radiotherapy (H-RT) (70 Gy in 28 fractions over 5.6 weeks). Median follow-up was 5.8 years. The estimated 5-year disease-free survival (DFS) was 85.3% (95% CI, 81.9–88.1) in the C-RT arm and 86.3% (95% CI, 83.1–89.0) in the H-RT arm. The DFS HR was 0.85 (95% CI, 0.64–1.14), and the pre-

defined noninferiority criterion that required that DFS outcomes be consistent with HR, 1.52 was met ( $P, .001$ ). Late grade 2 and 3 GI and genitourinary adverse events were increased (HR, 1.31–1.59) in patients who were treated with H-RT [144].

PROFIT – Prostate Fractionated Irradiation Trial, a multicenter randomized non-inferiority trial in intermediate-risk prostate cancer. Patients were allocated to conventional RT of 78 Gy in 39 fractions over 8 weeks or to hypofractionated RT of 60 Gy in 20 fractions over 4 weeks. Median follow-up was 6.0 years. The 5-year biochemical-clinical failure (BCF) disease-free survival was 85% in both arms (hazard ratio [short v standard], 0.96; 90% CI, 0.77– 1.2). No significant differences were detected between arms for grade > 2 late genitourinary and GI toxicity [145].

CHHiP is a randomised, phase 3, non-inferiority trial that recruited men with localised prostate cancer (pT1b–T3aN0M0). Patients were randomly assigned (1:1:1) to conventional (74 Gy delivered in 37 fractions over 7.4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over 3.8 weeks) all delivered with intensity-modulated techniques. Median follow-up was 62.4 months. The proportion of patients who were biochemical or clinical failure free at 5 years was 88.3% (95% CI 86.0–90.2) in the 74 Gy group, 90.6% (88.5–92.3) in the 60 Gy group, and 85.9% (83.4–88.0) in the 57 Gy group. 60 Gy was non-inferior to 74 Gy (HR 0.84 [90% CI 0.68–1.03], pNI = 0.0018) but non-inferiority could not be claimed for 57 Gy compared with 74 Gy (HR 1.20 [0.99–1.46], pNI = 0.48). Long-term side-effects were similar in the hypofractionated groups compared with the conventional group [146].

IMRT with integrated boost and stereotactic treatments are possible options, however caution is advised. A cost-effective alternative that exploits these radiobiological features is the combination of high-dose-rate brachytherapy that can be used in multiple settings (discussed later in chapter).

#### 26.7.3.1.1 Complementary Pelvic Lymph Nodes Irradiation and Androgen Deprivation

The indications for complementary irradiation of pelvic lymph nodes (common iliac, external iliac vein, internal iliac and obturator lymph node region) and use of androgen deprivation therapy are not clear. The pivotal randomized study testing the indication for irradiation of pelvic lymph nodes in combination with ADT was the RTOG 9413 trial [58]. In this trial the combined ADT and whole pelvic radiation therapy (WPRT) followed by a boost to the prostate improved progression-free survival (PFS) by 7% when compared to ADT and prostate-only (PO) RT (54 vs 47%,  $p = 0.022$ ). Moreover, this trial failed to demonstrate an added benefit from neoadjuvant and concurrent hormonal therapy (NCHT) when compared with adjuvant hormonal therapy (AHT) only, which was also a main point of evaluation in this trial. Patients enrolled in the study had localized PCa with PSA  $\leq 100$  ng/mL and an estimated risk of lymph node involvement >15% by the Roach Formula for

lymph node risk involvement (LN). In this study, 1323 patients were randomized in 4 arms: 2 in the WPRT group and 2 in the prostate-only irradiation (PORT) group; each group was subdivided in two ADT regimens: neoadjuvant and concurrent hormonal therapy (NCHT) versus adjuvant hormonal therapy (AHT). With a median follow-up of 59.5 months and when comparing all four arms, there was a progression-free difference in favor of WPRT + NCHT. The reported PFS for the four groups, WPRT + NCHT, PORT + NCHT, WPRT + AHT, and PORT + AHT were of 60% vs. 44% vs. 49% vs. 50%, respectively ( $p = 0.008$ ).

The Roach formula for lymph node risk involvement was simple and derived empirically from the Partin normogram. This formula, which is calculated as  $LN = (2/3) * PSA + 10 * (Gleason Score - 6)$ , was previously validated after reviewing the pathologic features of 282 patients who had undergone PR [59]. This means RTOG 9413 included high-risk but also a part of intermediate-risk patients which had a lymph node risk >15%.

The updated results from this trial reported no difference when comparing neoadjuvant vs. adjuvant hormone therapy and WPRT vs. PORT regarding PFS or OS. However, an unexpected difference was noted in pairwise comparison in favor of WPRT + NCHT. Patients receiving WPRT + NCHT had a better trend over PORT + NHT ( $p = 0.023$ ) and over WPRT + AHT ( $p = 0.014$ ), but not different when compared with PORT + AHT ( $p = 0.63$ ). The overall survival was statistically significantly different amongst the four arms ( $p = 0.027$ ) but pairwise comparison of the four arms in the study showed a worse trend for WPRT + AHT than every other arm of this study [60]. It should be reminded that this study is underpowered for arm vs arm analysis since it had assumed there was no interaction between field size and timing of hormone therapy. Also the p-values were not adjusted for multiple comparisons. Even so, this study demonstrated that aggressive treatment (combining WPRT and NCHT) should be offered to all high-risk and some intermediate-risk patients with a Roach formula for lymph node involvement >15%.

The RTOG 9413 also opened a series of questions regarding the indications and quality of WPRT (field site) and also indication and timing for hormone therapy. The Roach formula for lymph node involvement is still the standard discriminator for WPRT according to all evidence available. A good pelvic irradiation delineation is however a cornerstone [61]. Further results are awaited from the RTOG 0924 (NCT01368588).

In the 3D-CRT era and parallel to the race for better dose escalation techniques and hypo-fractionations schemes, a combined treatment with ADT was provided to high-risk patients to whom higher RT dose prescription was not possible [62]. Better outcomes were obtained if suppression started before RT and continued afterwards [63]. Clinically, the use of hormone therapy decreased PSA and prostate volume in short to medium-term (up to 33% volume decrease in 3–4 months) prior to radiation [64]; It also improved treatment response. A meta-analysis by Bria et al. [65] reports a significant improvement in terms of biochemical failure (RR 0.76; 95% CI 0.70–0.82;  $P < .0001$ ) and PFS (RR 0.81; 95% CI 0.71–0.93;  $P = .002$ ), with

absolute differences of 10% and 7.7%, respectively. ADT also improved cancer-specific survival (RR 0.76; 95% CI 0.69–0.83;  $P < .0001$ ) and OS (RR, 0.86; 95% CI, 0.80–0.93;  $P < .0001$ ), with absolute differences of 5.5% and 4.9%, respectively. Furthermore, in a metaanalysis by Nguyen et al., ADT was not associated with an increased risk of cardiovascular death for unfavorable-risk patients [66]. This means that ADT is to be considered in certain groups at risk. Trials such as the RTOG 86-10, RTOG 85-31, TROG 96.01, RTOG 9413 and EORTC 22863 confirmed benefit from the addition of ADT for patients with intermediate-risk, high-risk or those with lymph node involvement [67–70]. The specific duration of treatment is still under investigation, however therapy is usually recommended to begin at least 3 months before RT and continue for 2–3 years in high-risk patients and 3–6 months in intermediate-risk patients [36].

ADT in conjunction with RT is only applicable for intermediate, high-risk and node positive patients. WPRT is mandatory in all high-risk and some intermediate-risk patients.

### 26.7.3.2 Brachytherapy

Prostate brachytherapy (BT) consists in placing definitive or temporary radioactive sources inside the prostate gland by transperineal insertion. These sources have a short range emission which means that a higher dose is delivered to the prostate instead of other regional organs. The implantation is done under transrectal ultrasound (TRUS) guidance but the dosimetry calculations can be done by either TRUS or other imaging exams (CT or MRI).

BT is an appropriate option for low-risk PCa, especially for patients without LUTS and who haven't undergone a TURP, to decrease the risk of urinary symptoms [71].

Most of the data concerning low-risk PCa were obtained with low-dose-rate brachytherapy (LDR-BT) since high-dose-rate brachytherapy (HDR-BT) is a more recent technique. Also, the majority of studies using HDR-BT were performed for dose escalation with EBRT on high-risk groups. Nevertheless, there are studies that indicate that monotherapy with either LDR-BT or HDR-BT in low-risk PCa may have equally favorable outcomes [72, 73].

The LDR-BT techniques are mainly based on real time loading of definitive low-dose emission sources with longer half-life (I-125 and Pa-103) in the form of seeds that can be either inserted individually with an applicator (higher risk of migration or embolization) or deposited on a semirigid strand containing a preplanned number of seeds. This is a one-time procedure, however radioprotection measures are required for months after insertion of definitive seeds. It is also important to note that there could be significant variations of dose deposition due to migration of seeds, hence imaging control is necessary after 4 weeks to verify these events. The prescription dose in LDR-BT as monotherapy is of 145 Gy for I-125 or 125 Gy for Pa-103. In

case of combined therapy with EBRT (40–50 Gy) the prescription dose for I-125 or Pa-103 as a boost is lowered to 100 Gy and 90–110 Gy, respectively [36].

A systematic review from Rodrigues et al. [74] compared differences concerning efficacy between LDR-BT vs. EBRT and LDR-BT vs. RP for patients with low and intermediate risk. The use of I-125 and Pa-103 was also compared. All treatments were equally effective in terms of biochemical relapse-free survival, but differential toxicities were noted. Urinary irritation and rectal toxicity are more frequent in LDR-BT than RP, but urinary incontinence and sexual impotency occurred more often after RP. However, these differences diminished over time. LDR-BT conferred less risk of impotency and rectal morbidity than EBRT after 3 years of treatment. There were no differences between LDR-BT isotopes in terms of biochemical relapse-free survival and patient-reported outcomes. This systematic review had however relevant pitfalls. It included observational studies due to few RCT availability, and heterogeneity of EBRT dose treatments, quality of PR and LDR-BT, different definitions for biochemical relapse/recurrence and the use of neo-adjuvant ADT could have also biased this study.

The HDR-BT technique consists in temporary load of a high-dose emission source (e.g. Ir-192) after insertion of hollow catheters and the optimization of the dosimetric plan before treatment. This allows a reduction of the overall treatment time, eliminates the uncertainty related to volume changes, and improves accuracy of needle placement. Also radiobiology effectiveness is higher than with LDR-BT or external beam radiation due to PCa  $\alpha/\beta$  features. Furthermore, the same radioactive source can be used multiple times and for multiples patients. HDR-BT is also safer, with lesser need for radioprotection measures. On the other hand, HDR-BT requires fractionation to avoid normal tissue toxicity and is therefore a more time/resource consuming procedure as the patient must have the catheters and its template in place for a longer period of time. There are still points requiring standardization in this technique: the appropriate dose and fractionation schedule, differences in dosimetric results based on CT or ultrasound and, as a consequence, dose-volume histograms.

The studies using HDR-BT monotherapy in low and intermediate-risk PCa are evolving gradually with the use of hypofractionation schemes therefore delivering higher doses per fraction with equivalent outcomes and with similar to better toxicity profile (urinary, rectal and erectile function) when compared with LDR-BT [75].

The prescription dose for HDR-BT in monotherapy with Ir-192 is of 13.5 Gy x 2 fractions, twice-per-day with a minimum of 6 h apart. In case of combined treatment with HDR-BT as boost it is of 9.5–11.5 Gy x 2 fractions, 5.5–7.5 x 3 fractions or 4–6 Gy x 4 fractions [36].

It is common to recommend a trimodality treatment (EBRT+BT + ADT) in high-risk patients, since more aggressive treatment in these patients confer better outcomes in cancer control. Comorbidity assessment and clinical evaluation are required to confirm feasibility of this combined treatment.



## 26.8 General Toxicity in Localized PCa Therapy

To compare major toxicities and complications affecting quality of life (QoL) between different treatment options for localized prostate cancer, Sanda et al. [76] evaluated 1201 patients with PCa and 625 spouses/partners between 2003 to 2006. The following results were obtained:

- Urinary symptoms – At 1 year, moderate to severe distress from overall urinary symptoms was reported in 18% of patients in the BT group, 11% of those in the RT group and 7% in the radical prostatectomy group. Obstruction and urinary irritation were more frequent after RT, especially with BT, with a peak at 2 months. It developed less frequently 2 years after treatment. Incontinence was the main short-term problem after radical prostatectomy (about two thirds of the patients at 2 months) with 20% still requiring pads after 2 years.
- Bowel function – 10–20% of patients reported urgency and higher bowel frequency with radiotherapy treatments at 2 months after treatment. Symptoms persisted after 2 years in 7–16% cases. Bowel symptoms were rare after radical prostatectomy.
- Sexual function – Nearly 90% of patients suffered from sexual dysfunction after 2 months of radical prostatectomy and it was considered as a moderate or major problem in 60%. This dysfunction persisted after 2 years in 60% of cases (43% as moderate to major intensity). Sexual dysfunction also occurs for patients treated with RT, either EBRT or BT (60% erectile dysfunction at 2 months), which persisted at 2 years.

## 26.9 Adjuvant and Salvage Treatments

### 26.9.1 Adjuvant Management for Positive Surgical Margin or pT3 PCa

After surgical treatment some patients have higher risk of biochemical recurrence, which is observed in about 30–40% of all patients [77]. It tends to be higher in certain profiles of patients, most of them including positive margins, persistent PSA levels and at least one other high risk factor: positive lymph nodes, positive seminal vesicles (pT3b), extraprostatic extension (pT3a), preoperative PSA > 20 ng/ml or a Gleason score > 7 [78].

Three RCTs (SWOG 8794, EORTC 22911 and German ARO 96-02) concluded that adjuvant EBRT should be offered to patients with these risk factors in order to reduce biochemical recurrence/progression, metastasis occurrence and provide lon-

ger overall survival [79–81]. These include diffuse margins and persistent PSA levels. Recent updates consider that timing to deliver EBRT can be extended up to 6 months to 1 year after PR in order to recover from incontinence. It is important to remind that it should be started before PSA exceeds 1.5 ng/mL. The prescription dose is 64–70 Gy, although there are limitations due to toxicity to organs at risk which are, in most cases, inside the prostatic surgical bed. It is also recommended to insert clips during surgery when surgical margins are highly suspicious. The WPRT still remains controversial, especially in cases with positive lymph node(s) when extended PLND was not performed. Although NCCN guidelines consider that WPRT is not mandatory, clinical judgment is advised [36].

### **26.9.2 Management of Biochemical Recurrence with Local-Only Disease**

After definitive treatment, the criteria for biochemical recurrence will depend on the therapeutic procedure. After RP PSA should be undetectable after 1 month and recurrence is noted when 2 consecutive PSA values  $>0,2$  ng/mL are obtained in a 3 months interval. For radiation therapy (with or without ADT) there should always be a record of the PSA nadir (lowest PSA after radiation) since the actual notion of recurrence (Phoenix criteria) is based on PSA rise  $\geq 2$  ng/mL above the nadir.

It is important to define if the biochemical recurrence is due to local relapse or the presence of micro/macrometastasis. All clinical and pathological factors should be reviewed before definitive treatment and correlated with PSA kinetics, in order to determinate if there is a local or systemic recurrence. Depending on PSA behavior/kinetic 3 groups of patients might be found:

- Those in which PSA fails to fall to undetectable levels after RP;
- Those who show PSA fall with subsequent increase (recurrent disease as mentioned before)
- Patients with low yet persistent PSA.

Whereas the last group only requires PSA surveillance, the first two require restaging workup exams. Prostatic bed biopsy can be requested if there is suspicion of local recurrence. In cases with high suspicion, salvage EBRT to the prostate bed can be both therapeutic and diagnostic by PSA kinetics evaluation, namely downfall. EBRT treatment is most effective when pre-treatment PSA is below 0.5 ng/mL [82]. Adding WPRT and ADT are optional as in the adjuvant setting.

Biochemical recurrence after radiation therapy occurs in 20–50% of patients and only a minority will have a local-only relapse. Studies suggest that local salvage is beneficial for patients who had initially low-risk disease, pretreatment PSA velocity of  $<2.0$  ng/mL per year, PSA recurrence after  $>2$ –3 year and PSA doubling time  $>6$ –12 months, and most likely will have positive rebiopsy with a negative bone scan and pelvic imaging [83–85]. Patients with high risk PCa most likely have dis-

tant metastasis and are not candidates for local salvage and ADT can be advised. The best modality for local salvage is still under investigation because of patient selection and impartial accrual. There are three choices available for local salvage: salvage prostatectomy, salvage brachytherapy and salvage cryotherapy [83–85]. With the current data available salvage prostatectomy seems to be the best modality of choice [85].

## 26.10 Metastatic Prostate Cancer

Prostate cancer is mostly diagnosed as a localized disease, especially with the generalized use of PSA testing in asymptomatic patients. However, some patients present with metastatic disease, whereas others develop metastasis after treatment with curative intent.

Prostate cancer metastases frequently involve bone (predominantly axial skeleton, mainly lumbar vertebra [86]) and lymph nodes (regional and non-regional). Autopsy studies document bone involvement in 90% of these patients, however lung (46%), liver (25%), pleura (21%) and adrenal glands (13%) can also be affected [86]. The molecular mechanisms responsible for this pattern are unknown. Cancer cells in the bone induce tissue remodeling with predominance of bone formation, hence resulting in blastic (dense) lesions.

Metastatic prostate cancer can be divided into two groups: disease that has not been treated with androgen deprivation – metastatic castration-sensitive prostate cancer (mCSPC) – and disease that is resistant to such therapy – metastatic castration-resistant prostate cancer (mCRPC).

**Metastatic castration-sensitive prostate cancer** Metastatic castration-sensitive prostate cancer is generally considered to be incurable. Although localized prostate cancer has a 5-year survival rate of 100%, mCSPC has a 5-year survival rate of 29.8% [131]. The treatment of mCSPC has significantly changed over the past 5 years. The backbone of treatment of mCSPC is androgen deprivation therapy (ADT) to deprive prostate cancer cells of growth-stimulating androgens. Since 2015, two clinical trials, CHAARTED and STAMPEDE arm C, demonstrated that up-front docetaxel plus ADT improves overall survival (OS) in patients with mCSPC [132, 133]. Then, in 2017, two clinical trials, LATITUDE and STAMPEDE arm G, showed that up-front abiraterone plus prednisone plus ADT improves OS to a similar degree as docetaxel plus ADT did [134, 135]. To date, we have no formally published head-to-head comparisons of ADT plus docetaxel versus ADT plus abiraterone. We will start by discussing the role and different modalities of ADT. Then we will analyze the more recent results that changed the treatment paradigm for mCSPC, including ADT plus docetaxel, ADT plus abiraterone. We will finish by giving a broad glance at the novel combinations currently being investigated.

**Androgen-Deprivation Therapy** ADT has an essential role in the treatment of newly diagnosed metastatic PCa patients given that most prostate cancers are androgen dependent [87]. While palliative, it is effective controlling disease growth and improving patients' quality of life. Most androgens (around 90%) are produced in the testes, while the remaining are produced in the adrenal glands. The testicular production of androgens is controlled by the hypothalamic-pituitary axis, specifically in response to luteinizing hormone (LH) released from the anterior pituitary gland. ADT is obtained either by surgical orchiectomy or medical castration to reach castrate levels of testosterone.

Surgical castration by bilateral orchiectomy induces a rapid and sustained decline in serum testosterone with clinical effectiveness in controlling metastatic prostate cancer [88]. The main advantages of surgical approach include immediate onset of action, no tumor flare reaction (discussed ahead), therapeutic adherence, fewer subsequent clinical visits and inferior total overall costs. However, the psychological impact of surgical testes removal limits its use.

Medical castration, the most frequent option, is achieved through the manipulation of the hypothalamic-pituitary axis with gonadotropin releasing hormone (GnRH) agonists or antagonists.

GnRH agonists, which include goserelin, leuprolid and others (triptorelin, buse-relin and histrelin), induce an acute (1–2 weeks) increase in serum LH and hence testosterone. However, the continued agonism of GnRH receptors in the pituitary gland induces an internalization/downregulation of GnRH receptors, which results in the profound decline in LH and testosterone and ultimately a reversible chemical castration. Testosterone levels are within the castrate range in 3–4 weeks [87]. The acute increase in serum testosterone (first 2–3 weeks) may induce a “disease flare” with tumor growth and worsening disease signs and symptoms (p.e. bone pain or urinary obstruction). Therefore, monotherapy with GnRH agonists is contraindicated in the setting of impending spinal cord compression, uncontrolled bone pain or urinary obstruction (a minority of the patients). To overcome this limitation it is recommended to administer nonsteroidal antiandrogens (flutamide, bicalutamide, or nilutamide) for a short period before the introduction of GnRH agonists and concurrent administration for 2 weeks after [87]. Another available option is the use of GnRH antagonists, as degarelix (240 mg SubQ loading dose followed by 80 mg SubQ every 28 days, 28 days after initial loading dose). Degarelix needs however more frequent administrations, which increases costs and may contribute to impair adherence.

The therapeutic goal is to achieve castration levels of testosterone, historically defined as <50 ng/dl. This reference value is supported by clinical practice guidelines (namely from the NCCN) even though most patients may decline to even lower values (<20 ng/dl [89]).

A meta-analysis of the available evidence [90] including information from 10 trials with 1908 patients compared the effectiveness of GnRH agonists to orchiectomy and concluded that these options are equivalent regarding overall survival (HR 1.1262; 95% CI, 0.915–1.386).

Besides short term association between GnRH agonists and antiandrogens to overcome “tumor flare”, long term combined androgen blockage (CAB) has been tested to improve disease outcomes. The additive effect would come from the blockage of the adrenal testosterone. A large meta-analysis (data from 27 randomized trials including 8275 men) documented a borderline statistical and clinical significant reduction in mortality with CAB when compared to monotherapy (72.4% crude mortality for monotherapy vs. 70.4% with combined blockage; relative risk 0.97; 95% CI 0.94–1.00) [91]. This borderline benefit needs however to be balanced against the great toxicity and extraordinarily poor cost-effectiveness [87]. Some of the documented side effects of CAB compared to monotherapy include diarrhea (10% v 2%), abdominal (gastrointestinal) pain (7% v 2%) and nonspecific ophthalmologic events (29% v 5%) [92].

Despite the effective control of metastatic prostate cancer ADT induces relevant side effects:

- Sexual dysfunction, manifested by loss of libido and erectile dysfunction, which develops in the majority of the patients during the first months of therapy.
- Osteoporosis and bone fractures. ADT increases bone metabolism and decreases bone mineral density, hence increasing the risk of bone fractures. Osteoporosis-related bone fractures occur in up to 20% of the patients under ADT after 5 years of therapy (as compared with 12.6% of those not receiving androgen-deprivation therapy) [93] Frequent weight bearing exercise, supplementation with calcium (1000–1200 mg daily) and vitamin D (800 to 1000 international units daily), smoking cessation, reduced alcohol and caffeine consumption help prevent osteoporotic fractures. Osteoclast inhibition with either bisphosphonates or denosumab is indicated for patients with bone metastasis (discussed ahead), however these agents also improve bone health in patients at increased risk of fracture due to accelerated bone loss (NCCN guidelines recommend bone modifying agents for prostate cancer patients with 3-years probability of fracture  $\geq 3\%$  or 10-years probability  $\geq 20\%$ , as assessed by FRAX score).
- Vasomotor symptoms, specifically hot flashes. Medroxyprogesterone, cyproterone acetate, venlafaxine and gabapentin have all shown efficacy controlling hot flashes.
- Reconfiguration of body composition and metabolism. ADT therapy decreases lean body mass and increases fat mass. A reduction in insulin sensitivity [94] and increase in total cholesterol, LDL cholesterol and non-HDL cholesterol is also noted [95]. These are important risk factors for cardiovascular disease. Other important body modifications include gynecomastia, decreased penile and testicular size and thinning of body hair.
- Fatigue, depression and cognitive decline have also been documented.

Intermittent ADT was proposed as a strategy to minimize ADT toxicity.

## 26.11 Metastatic Castration-Resistant Prostate Cancer

Over time, nearly all men progress under standard medical ADT. Prostate cancer is considered castration-resistant (CRPC) when documented progression of cancer (rise in PSA, new metastasis or progression of existing metastasis) occurs despite successful medical or surgical ADT (resulting in serum testosterone in the castration level, i.e. <50 ng/dL). Most patients with CRPC are diagnosed after an asymptomatic elevation of PSA.

In CRPC the androgen receptor (AR) is reactivated even under GnRH agonism and direct AR antagonism. This phenomenon is explained by several tumoral adaptive alterations, as increased AR expression, AR mutations enhancing activation by weak androgens and even AR antagonists, increased expression of transcriptional coactivator proteins, activation of signal transduction pathways that can enhance AR responses to low levels of androgens and finally tumoral intracellular synthesis of testosterone and DHT from weak adrenal androgens [99]. There can also be androgen-receptor splice variants, the most common of which is AR-V7, in this variant the androgen-receptor ligand-binding regulatory domain is deleted. The constitutive receptor-mediated transcriptional activation that occur despite the absence of ligand can lead to resistance to drugs targeting the androgen axis [139].

Several treatment options are available for castration-resistant prostate cancer. Unfortunately, no head-to-head trials between these agents are available to allow a sequential approach that would best guide treatment options. Treatment sequence depends on best clinical judgment (based on type and extent of affected organs and tumor progression rate), local availability of therapies and patients' preference.

Secondary hormonal therapies are historically the first option in asymptomatic CRPC, however none of these have demonstrated improved survival [100]. Some alternatives include the combination of GnRH agonists with antiandrogens, antiandrogens withdrawal, ketoconazole, glucocorticoids or estrogens.

- Antiandrogens block the androgen receptor competing with dihydrotestosterone. These agents include bicalutamide (50 mg once daily), cyproterone acetate (200–300 mg daily in 2–3 divided doses), flutamide (250 mg 3 times daily) and nilutamide (300 mg once daily for 30 days followed by 150 mg once daily). There is no randomized trial comparing different antiandrogen drugs. Hepatotoxicity (p.e. hepatitis) is a feared secondary effect (most commonly with flutamide). For patients progressing under treatment with GnRH agonists and antiandrogens, antiandrogens withdrawal may result in a clinical/biochemical response.
- Glucocorticoids, including prednisone (5 mg twice daily), dexamethasone (0.5–2 mg per day) or hydrocortisone (40 mg per day) reduce the release of ACTH and hence of adrenal androgens. Steroids are associated with a plethora of side effects (metabolic, immune, cutaneous, gastro-intestinal and others).
- Diethylstilbestrol (DES; 1 mg per day) competes with androgens for the androgen receptor and has a direct cytotoxic action in prostatic cancer cells [101].

- Ketoconazol (200–400 mg three times per day on empty stomach), a CYP17A1 inhibitor, blocks the adrenal production of androgens [102]. Nausea and vomiting are common side effects. Elevated liver enzymes and adrenal insufficiency are of cornerstone relevance. Due to safety concerns ketoconazole was removed from the European Union market and its use restricted in the US [103, 104]. Patients receiving ketoconazole should have regular liver enzymes monitoring and concurrent administration of hydrocortisone.

Recent research contributed to the development of treatment options that prolong patients' survival besides symptomatic control. These agents include drugs targeting extragonadal biosynthesis of androgen or targeting the AR (abiraterone and enzalutamide), chemotherapy (docetaxel and cabazitaxel), immunotherapy (sipuleucel-T) and bone acting radiopharmaceuticals (radium-223). Current evidence demonstrates the applicability of some of these new agents also in the context of metastatic castration-sensitive prostate cancer.

Abiraterone (1000 mg once daily in combination with prednisone) is a potent and selective inhibitor of cytochrome P450 17A1, thus blocking the androgen synthesis in the testes, adrenal gland and inside tumor cells [105, 106]. Abiraterone, which is available as prodrug referred as abiraterone acetate, demonstrated in phase III trials its effectiveness in patients with CRPC before or after chemotherapy treatment with docetaxel [107, 108]. The pivotal abiraterone phase III trial (COU-AA-301 trial [107]) recruited asymptomatic or mildly symptomatic patients who had previously received docetaxel and tested prednisone (5 mg twice daily) with either abiraterone acetate (1000 mg/day) or placebo in 1195 patients (2:1 randomization). The study was prematurely unblinded after an interim analysis favouring abiraterone. With a median follow-up of 12.8 months overall survival (primary endpoint) was longer for abiraterone plus prednisone group (14.8 vs. 10.9 months; 35% reduction in the risk of death; HR 0.65; 95% CI 0.54 to 0.77). Time to PSA progression was also favourable to abiraterone (10.2 months vs. 6.6 months). Regarding safety, abiraterone was globally well tolerated. Mineralocorticoid related adverse events (specifically fluid retention, edema and hypokalemia), cardiac events (specially tachycardia) and hepatotoxicity (increased liver enzymes) occurred at a higher rate in patients receiving abiraterone. Noteworthy, subjects with heart failure NYHA III-IV/ejection fraction <50% and those previously exposed to ketoconazol were excluded from this trial. As previously referred, abiraterone was also tested in 1088 men with asymptomatic or mildly symptomatic not previously exposed to docetaxel (COU-AA-302 trial [108]). This trial was prematurely stopped after a interim analysis (at 43% of the expected deaths occurred) favouring abiraterone. In a follow-up analysis [109] at 55% of OS events and median follow-up of 27.1 months, abiraterone plus prednisone showed a trend towards improved overall survival when compared to prednisone alone (35.3 vs. 30.1 months; HR 0.79; 95% CI 0.66–0.96; pre-specified efficacy boundary not crossed). The other primary endpoint, radiographic progression-free survival (rPFS), was significantly improved for abiraterone (16.5 vs. 8.3 months; HR 0.53; 95% CI 0.45–0.62). These results granted extended approval of abiraterone prior to chemotherapy for mCRPC patients in the US and EU.

Enzalutamide (160 mg once daily) is a potent androgen receptor antagonist. Unlike bicalutamide, enzalutamide reduces the nuclear-to-cytoplasmic AR ratio and appears to prevent the binding of AR to DNA [110]. The AFFIRM trial demonstrated the effectiveness of enzalutamide in patients with CRPC after chemotherapy with docetaxel [111]. This pivotal phase III trial recruited patients who had previously received docetaxel and tested 160 mg of enzalutamide or placebo in 1199 patients (2:1 randomization). The use of corticosteroids was allowed but not mandatory. The study was also prematurely unblinded after an interim analysis favouring enzalutamide. Overall survival (primary endpoint) was longer for enzalutamide treated patients (18.4 vs. 13.6 months for placebo; 36.9% reduction in the risk of death; HR 0.631; 95% CI 0.53–0.75). Time to PSA progression also favoured enzalutamide (8.3 vs. 3.0 months;  $P < 0.001$ ). Patients receiving enzalutamide had more frequently hypertension, diarrhea, hot flashes, musculoskeletal pain and headache. Seizures were reported during early administration of enzalutamide in 0.6% of the patients (5 in 800). Following, patients with predisposing factors for seizures were excluded from the trial, therefore this agent should be used with caution in these patients. Enzalutamide was also tested in chemotherapy-naive patients (PREVAIL trial [112]). This trial was prematurely stopped after a interim analysis at 539 from the planned 765 deaths showing a statistically significant benefit of enzalutamide over placebo in OS (estimated median OS 32.4 vs. 30.2 months for placebo arm; HR 0.70; 95% CI: 0.59–0.83;  $P < 0.0001$ ) and risk of radiographic progression or death (median not reached vs. 3.9 months for placebo arm; HR 0.19; 95% CI: 0.15–0.23;  $P < 0.0001$ ).

The subsequent use of abiraterone post enzalutamide or vice versa in patients already treated with docetaxel is of limited efficacy [113, 114]. However, exploratory findings rose the rational for concomitant treatment with abiraterone and enzalutamide [115]. A trial (NCT01949337) is currently testing this synergistic approach.

Chemotherapy is a valid and long-used therapeutic option for mCRPC. However, only more recent taxane-based regimens (docetaxel and cabazitaxel) demonstrated an improved survival. Until then mitoxantrone plus a corticosteroid was the reference treatment. This combination was approved in 1996 based on improved symptomatic control, namely pain reduction [116]. Subsequent studies demonstrated further benefit in terms of response, time to disease progression and time to treatment failure but never an improvement in overall survival [117, 118].

Docetaxel was the first taxane-based chemotherapy to be approved and is the standard first-line chemotherapy drug in mCRPC. Docetaxel was approved based on the pivotal trial TAX 327 [119] that recruited 1006 men with mCRPC to receive prednisone (5 mg twice daily) with either mitoxantrone (12 mg/m<sup>2</sup> every 3 weeks), docetaxel every 3 weeks (75 mg/m<sup>2</sup>) or docetaxel weekly (30 mg/m<sup>2</sup> for five of every 6 weeks). An updated follow-up version [120] after 867 overall survival events (primary endpoint) demonstrated benefit from docetaxel every 3 weeks (median survival time 19.2 vs. 17.8 vs. 16.3 months in the every 3 weeks docetaxel, weekly and mitoxantrone groups, respectively; HR 0.79 for docetaxel every 3 weeks vs. mitoxantrone;  $p = 0.004$ ). Weekly docetaxel brought no overall survival improve-



ment when compared to mitoxantrone. When compared to mitoxantrone, patients treated with docetaxel every 3 weeks had more frequent neutropenia (but not febrile neutropenia), sensory neuropathy, fatigue, alopecia, diarrhea and peripheral edema. For patients unlikely to tolerate docetaxel every 3 weeks (75 mg/m<sup>2</sup>), a regimen using docetaxel every 2 weeks (50 mg/m<sup>2</sup>) showed better tolerability (5.6 vs. 4.9 months to treatment failure,  $p = 0.014$ ) and improved median overall survival (19.5 vs 17.0 months; HR 1.4; 95% CI 1.1–1.8) [121]. Further data is needed to generalize this regimen schedule.

The correct timing for administration of chemotherapy in mCRPC is not completely clear. A general approach is to follow the inclusion criteria from the pivotal trial of docetaxel, which recruited patients who had progressed during hormonal therapy and had a Karnofsky performance-status score of at least 60%. Other indications include symptomatic patients or with extensive metastasis, rapid PSA doubling time, high Gleason score or short-term response to primary ADT [122].

Cabazitaxel was the second taxane-based chemotherapy and is the standard second-line chemotherapy agent in mCRPC. Cabazitaxel was approved based on the pivotal trial TROPIC that recruited men with mCRPC who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen [123]. In this phase III trial, 755 men were treated with prednisone (10 mg daily) with either mitoxantrone (12 mg/m<sup>2</sup> every 3 weeks) or cabazitaxel (25 mg/m<sup>2</sup> every 3 weeks). With a median follow-up of 12.8 months, overall survival (primary endpoint) favoured cabazitaxel group (15.1 vs. 12.7 months; HR 0.70; 95% CI 0.59–0.83). Neutropenia was a common finding in both arms, but more frequently with cabazitaxel (grade 3/4 in 81.7% vs. 58.0% in the mitoxantrone arm) where febrile neutropenia occurred in 8% (vs. 1% with mitoxantrone arm). The authors recommend careful monitoring of blood counts to determine if initiation of G-CSF and/or dosage modification is needed. The phase III PROSELICA study, with a non-inferiority design, tested a lower dose of cabazitaxel (20 mg/m<sup>2</sup> of cabazitaxel compared with 25 mg/m<sup>2</sup>) as a strategy to reduce myelotoxicity.

Overall, 1200 patients were randomly assigned (C20,  $n = 598$ ; C25,  $n = 602$ ). Median OS was 13.4 months for C20 and 14.5 months for C25 (HR, 1.024). The upper boundary of the HR CI was 1.184 (less than the 1.214 noninferiority margin). Significant differences were observed in favor of C25 for PSA response (C20, 29.5%; C25, 42.9%; nominal  $P, .001$ ) and time to PSA progression (median: C20, 5.7 months; C25, 6.8 months; HR for C20 v C25, 1.195; 95% CI, 1.025–1.393). Health-related quality of life did not differ between cohorts. Rates of grade 3 or 4 treatment-emergent adverse events were 39.7% for C20 and 54.5% for C25. In this trial the noninferiority end point was met (C20 maintained  $\geq 50\%$  of the OS benefit of C25 versus mitoxantrone in TROPIC). However secondary efficacy end points favored C25. As expected, fewer adverse events were observed in the reduced dose arm [140].

Other commonly reported adverse events with cabazitaxel were diarrhea (47 vs. 11%) and peripheral neuropathy (14 vs. 3%; 1% grade 3 in each group).

Cabazitaxel was also tested in first-line therapy of mCRPC in comparison with docetaxel in the FIRSTANA trial. In this randomized phase III trial 1168 patients were randomly assigned 1:1:1 to receive C20, C25, or D75 intravenously every 3 weeks plus daily prednisone. The primary end point was OS. Secondary end points included safety; progression-free survival (PFS); tumor, prostate-specific antigen, and pain response; pharmacokinetics; and health-related quality of life. Median OS was 24.5 months with C20, 25.2 months with C25, and 24.3 months with D75. Hazard ratio for C20 versus D75 was 1.01 (95% CI, 0.85–1.20;  $P = .997$ ), and hazard ratio for C25 versus D75 was 0.97 (95% CI, 0.82–1.16;  $P = .757$ ). Median PFS was 4.4 months with C20, 5.1 months with C25, and 5.3 months with D75, with no significant differences between treatment arms. Radiographic tumor responses were numerically higher for C25 (41.6%) versus D75 (30.9%; nominal  $P = .037$ , without multiplicity test adjustment). Rates of grade 3 or 4 treatment-emergent adverse events were 41.2%, 60.1%, and 46.0% for C20, C25, and D75, respectively. Febrile neutropenia, diarrhea, and hematuria were more frequent with C25; peripheral neuropathy, peripheral edema, alopecia, and nail disorders were more frequent with D75. This trial showed that both dosages of cabazitaxel did not demonstrate superiority for OS versus D75 in patients with chemotherapy-naïve mCRPC [141].

Sipuleucel-T is cellular immunotherapy that uses autologous peripheral-blood mononuclear cells (PBMCs) with antigen-presenting cells (APCs) that have been activated *ex vivo* with a recombinant fusion protein identified as PA2024. PA2024 is dimmer composed of prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor. The first component acts as the antigen and the second as an immune-cell activator. This therapeutic cancer vaccine was tested in a phase III trial (IMPACT trial [124]) that randomized 512 men with minimally symptomatic metastatic castration-resistant prostate cancer for sipuleucel-T or placebo (2:1 randomization) every 2 weeks, for a total of three infusions. After a median follow-up of 34.1 months, men in the sipuleucel-T group had a longer overall survival (25.8 vs. 21.7 months for placebo; 22% reduction in the risk of death; adjusted HR 0.78; 95% CI 0.61–0.98). No significant difference was observed in PFS or PSA response rate, which can jeopardize the assessment of treatment response in patients with this agent. Sipuleucel-T is very well tolerated; however chills (in 51.2%), fever (22.5%), fatigue (16.0%), nausea (14.2%), and headache (10.7%) were documented. Sipuleucel-T should be used cautiously in patients with visceral metastasis given that these patients were excluded from the IMPACT trial.

As previously referred, osteoblastic bone lesions are the most common site of metastases in prostate cancer patients. Effective therapeutic strategies include EBRT, bone-targeted radiopharmaceuticals and bone modifying agents (bisphosphonates and denosumab) – only approved for mCRPC – these treatment strategies will be discussed elsewhere (vide bone metastasis chapter). There is a specific bone acting radiopharmaceutical that also has an impact on survival – Radium-223 – this agent will also be discussed in the chapter dedicated to bone metastasis.(vide bone metastasis chapter).

**Genomic Alterations and Possible New Therapeutic Targets in mCRPC** The most common genomic alterations in patients with mCRPC involve the androgen

receptor (in >60% of patients), but p53 mutations or deletions are also common and can be concurrent with RB1 loss, together leading to lineage plasticity from luminal to basal phenotypes. The loss of tumor suppressor PTEN, as well as other aberrations activating AKT signaling can occur in approximately 40% of the patients. There is a trial ongoing targeting especial this subset of patients (NCT03072238). Deleterious somatic and germline aberrations in DNA-repair genes are common in men with metastatic, castration-resistant prostate cancer. Homologous recombination repair defects, the most common of which is BRCA2, may confer sensitivity to poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors and platinum based therapy. Multiple trials of PARP inhibitors in this patient population are ongoing (NCT02975934, NCT02987543, NCT02854436) [139].

## 26.12 Neuroendocrine Prostate Cancer

Neuroendocrine prostate cancer (NEPC) is an aggressive subtype of disease, which may arise either at first diagnosis or more frequently after hormone therapy for prostate adenocarcinoma. This disease subtype is characterized by an aggressive phenotype/high tumor burden, namely with visceral involvement, low or modestly elevated PSA and elevated serum markers of neuroendocrine differentiation (*i.e.* chromogranin A and neuron-specific enolase). Patients with NEPC have a dismal prognosis with nearly all patients dying within 1 year [126]. This subtype of prostate cancer seems to better respond to platinum-based chemotherapy regimens, similar to small cell lung carcinoma [127].

## 26.13 Follow-Up of Patients during Treatment and Surveillance in the Context of Prostate Cancer

Patients' follow-up after primary curative intervention was designed for the detection of local recurrences, metastasis and treatment complications. On the other hand, metastatic patients need to be monitored for treatment efficacy and safety.

There are no randomized trials to support an optimal surveillance strategy. NCCN guidelines recommend the following strategy:

- Patients treated with initial definitive therapy:
  - PSA testing every 6–12 months for 5 years, then every year
  - The clarification of disease status may imply PSA testing as every 3 months
  - Digital rectal examination every year (can be omitted if PSA undetectable)
- Patients with N1 or M1 disease (stage IV)

- Physical examination every 3–6 months
- PSA testing every 3–6 months

Imaging studies should be performed as clinically indicated, based on individual risk, age, PSA doubling time, Gleason score and overall health.

Some groups [125], based on the Prostate Cancer Working Group 2 consensus criteria, selected some indicators of disease manifestation and treatment effectiveness. Serially monitoring in disease manifestations documented at baseline with the same modality used before treatment is recommended. Indicators of failure in treatment effectiveness include:

- (a) PSA elevation of 25% or an absolute increase of 2 ng/mL or more from the nadir;
- (b) Progression in the soft tissue component as defined by RECIST criteria;
- (c) Bone scan progression needs either two new lesions noted on the first on-treatment scan followed by two additional lesions on the next scan (performed 6 weeks or longer after the first scan) or two new lesions seen on any scan after the first on-treatment scan that are confirmed on a subsequent scan;
- (d) Development of bone metastasis and SREs;
- (e) Uncontrolled symptoms, as pain, or more broadly degradation in patient-reported outcomes.

In the case of discordance between outcomes (p.e. rising PSA without changes in other indicators) treatment should continue until a clear pattern is registered. Moreover, treating a patient at least for 12 weeks before judging treatment effectiveness is recommended.

## 26.14 Prognosis

**Androgen-Deprivation Therapy Plus Docetaxel** Docetaxel is a taxane that binds tubulin and stabilizes microtubules, thereby inhibiting mitosis. This agent has an established role in the treatment on mCRPC, however in an attempt to improve the prognosis of patients with mCSPC this agent has been tested in combination to ADT in two large scale randomized controlled trials (RCT). In the CHAARTED trial a total of 790 patients with de novo metastatic disease were randomized to receive either ADT plus docetaxel (at a dose of 75 mg per square meter of body-surface area every 3 weeks for six cycles) or ADT alone. After a median follow-up of 28.9 months, the median overall survival was 13.6 months longer with ADT plus docetaxel (combination therapy) than with ADT alone (57.6 months vs. 44.0 months; hazard ratio for death in the combination group, 0.61; 95% confidence interval [CI], 0.47–0.80;  $P < 0.001$ ). The median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the combination group, as compared with 11.7 months in the ADT-alone group (hazard ratio, 0.61; 95% CI, 0.51–0.72;  $P < 0.001$ ). The rate of a prostate-specific antigen level of less than 0.2

ng per milliliter at 12 months was 27.7% in the combination group versus 16.8% in the ADT-alone group ( $P < 0.001$ ). In the combination group, the rate of grade 3 or 4 febrile neutropenia was 6.2%, the rate of grade 3 or 4 infection with neutropenia was 2.3%, and the rate of grade 3 sensory neuropathy and of grade 3 motor neuropathy was 0.5%. In this study subanalyzed patients with low and high-volume disease (defined as disease involving any visceral metastases or at least four bone lesions with at least one extra-axial). A considerable benefit was noted for patients with high-volume disease (hazard ratio for death, 0.61; 95% CI, 0.45–0.81;  $P < 0.001$ ; median overall survival, 49.2 vs. 32.2 months) while the subset of patients with low-volume disease had fewer events, with survival data not reaching statistical significance [132]. The STAMPEDE trial is a randomised controlled trial using a multiarm, multistage platform design. In this trial randomly 2962 men with locally advanced or mHSPC (61%) were randomly assigned to receive ADT alone (arm A); ADT plus zoledronic acid (arm B); ADT plus docetaxel (arm C); or ADT, docetaxel, and zoledronic acid (arm E). ADT plus docetaxel significantly improved median OS compared with ADT alone in STAMPEDE arm C (81 months vs. 71.3 months; HR 0.78; 95% CI, 0.66–0.93). ADT plus docetaxel also improved median failure-free survival compared with ADT alone (37 months vs. 20 months; HR 0.61; 95% CI, 0.53–0.70). As was seen in the other trials, more patients in the ADT plus docetaxel arm reported grade 3/4 adverse events than did those receiving ADT alone (39% vs. 17%), and one treatment-related death occurred in the ADT plus docetaxel cohort. Unfortunately, STAMPEDE did not report outcomes by volume of disease [133]. These trials and subsequent meta-analysis established ADT plus docetaxel as a standard of care for fit patients with high-volume mCSPC.

**Androgen-Deprivation Therapy Plus Abiraterone Plus Prednisone** Similar to docetaxel, abiraterone acetate was initially approved for the treatment of mCRPC, it acts by inhibiting androgenic steroid synthesis. To date, two clinical trials studying abiraterone in mCSPC have been reported, LATITUDE and STAMPEDE arm G. LATITUDE was a phase III clinical trial that randomly assigned 1199 men with mCSPC to receive ADT plus abiraterone (1000 mg daily) and prednisone (5 mg daily) or ADT alone. To be included in the trial, men with mCSPC needed to have at least two high-risk prognostic factors, including a Gleason score  $\geq 8$ , presence of at least three bone lesions, or measurable visceral metastases. LATITUDE was powered to measure two primary endpoints: median OS and radiographic PFS. ADT plus abiraterone significantly improved median OS (not reached vs. 34.7 months; HR 0.62; 95% CI, 0.51–0.76) and median radiographic PFS (33.0 vs. 14.8 months; HR 0.47; 95% CI, 0.39–0.55). In terms of toxicity, grade 3/4 adverse events were more common in the ADT plus abiraterone arm (63% vs. 48%). The most frequently reported grade 3/4 adverse events in the abiraterone arm were mineralocorticoid-related hypertension (20%), hypokalemia (11%), and increased alanine aminotransferase levels (5%) [134]. STAMPEDE arm G was a phase III clinical trial that included multiple cohorts of patients with advanced prostate cancer, including mCSPC, node-positive disease, or high-risk locally advanced disease. In total, 1917 men with advanced prostate cancer were randomly assigned to receive ADT plus

1000 mg of abiraterone plus 5 mg of prednisolone or ADT alone. Of these 1917 men, 941 had newly diagnosed mCSPC. In the overall cohort, ADT plus abiraterone demonstrated a strong OS advantage compared with ADT (83% vs. 76%; HR 0.63; 95% CI, 0.52–0.76) and better 3-year failure-free survival (75% vs. 45%; HR 0.29; 95% CI, 0.25–0.34). In patients with mCSPC, the effect of ADT plus abiraterone on OS and failure-free survival remained true. As was seen in LATITUDE, the incidence of grade 3/4 adverse events was higher in the ADT plus abiraterone group than in the ADT alone group (47% vs. 33 %) [135].

**Local Treatment in Metastatic Disease** Two phase III trials have studied the addition of prostate radiotherapy (RT) to standard systemic treatment in men with newly diagnosed metastatic disease. The STAMPEDE trial showed that RT to the prostate did not improve overall survival (OS) for unselected patients. However, a pre-specified subgroup analysis showed that RT did improve OS (from 73% to 81% at 3 years) in those with a low metastatic burden (defined according to the CHARTED criteria) [136]. In the HORRAD trial the results were consistent with STAMPEDE: there was no OS benefit in unselected patients [137]. In both trials, standard systemic treatment was androgen deprivation therapy (ADT) alone for the majority of patients. Meta-analysis of these two trials found that prostate RT improved 3-year OS by 7% for men with less than five metastases on baseline bone scan [138]. In the past few years, mCSPC therapy landscape has suffered numerous alterations and there are still multiple trials ongoing. (Table 26.3) Table 26.5 – Ongoing Phase III Clinical Trial in Metastatic Castration-Sensitive Prostate Cancer [131]. The prognosis of metastatic prostate cancer is closely linked to PSA response following therapy initiation. PSA nadir, i.e. the lowest PSA determination, following ADT deprivation >0.2 ng/ml is associated with shorter overall survival (OS) [97]. Those with PSA nadir between 0.2 and 4 ng/ml have an intermediate prognosis, while those with PSA nadir >4 have considerably worse OS outcomes [98]. One study obtained survival times of 13, 44 and 75 months for PSA nadir > 4, between 0.2–4

**Table 26.5** Ongoing phase III clinical trial in metastatic castration-sensitive prostate cancer

Trial Name	Arms	No. of patients	Primary endpoint	Clinicaltrials.gov identifier
PEACE-1	ADT ± doce, ± RT, ± abi	916	rPFS, OS	NCT01957436
SWOG-1216	ADT + TAK-700 vs. bicalutamide	1304	OS	NCT01809691
ARASENS	ADT + doce + ODM-201 vs. placebo	1300	OS	NCT02799602
ENZA-MET	ADT ± doce + enza vs. NSAA	1100	OS	NCT02446405
ARCHES	ADT ± doce + enza vs. placebo	1100	rPFS	NCT02677896
STAMPEDE arm J	ADT ± doce, ± RT, ± abi + enza	1800	OS	NCT00268476
TITAN	ADT ± doce + apa vs. placebo	1000	rPFS, OS	NCT02489318

Abbreviations: ADT androgen-deprivation therapy, doce docetaxel, RT radiotherapy, abi abiraterone acetate, rPFS radiographic progression-free survival, OS overall survival, enza enzalutamide, NSAA nonsteroidal androgen antagonist, apa apalutamide

and  $<0.2$  ng/ml, respectively [98]. Gleason score  $> 7$  is also associated with worse OS outcome [97].

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# Chapter 27

## Kidney Cancer: From Basics to Immunotherapy



Audrey Cabral Ferreira de Oliveira and Fernando Nunes Galvão de Oliveira

**Abstract** Renal cell carcinoma (RCC) accounts for 80–85% of primary renal malignancies. The clear cell subtype is the most common and best represented in clinical trials. The detection of other histologies of renal tumors and various surgical strategies combined with the understanding of molecular biology and immunology directed to VHL-HIF-VEGF, mTOR and PD-L1 have modified the natural history of this disease and brought new dynamics to the algorithm of treatment of this disease. Our purpose is to review the biological mechanisms and present the results of important clinical trials in the area of kidney cancer.

**Keywords** Vascular endothelial growth factor · Cancer immunotherapy · Renal cell carcinoma · Metastatic renal cell carcinoma · Clear cell renal cell carcinoma

### Abbreviations

CT	Computed Tomography
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
DFS	Disease Free survival
EORTC	European Organization for Research and Treatment of Cancer
FH	fumarate hydrate
HIF	Hypoxia-inducible factor
IFN	Interferon
IL-2	interleukin 2
IMDC	International mRCC Database Consortium
LDH	lactate dehydrogenase
MRI	Magnetic resonance imaging

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mTOR	mammalian target of rapamycin
NVL	Normal value limit
OS	Overall survival
PDGF	Platelet-derived growth factor
PD-L1	programmed death ligand 1
PFS	Progression Free Survival
RCC	Renal Cell Carcinoma
SEER	Surveillance, Epidemiology, and End Results
TNM	tumor node metastasis
USG	ultrasonography
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau

## 27.1 Introduction

RCC represents 80–85% of primary renal malignancies, accounting for 2% of all cancer deaths [1]. In the last 50 years, the incidence increased threefold more than mortality and 5-year survival doubled from 34% in 1954 to 73% from 2005 to 2011. This fact is probably due to the detection of early tumors and surgical treatment, which is the only therapeutic modality with curative intent [2, 3].

Clear cell carcinoma is the most common histological subtype and best represented in clinical trials, accounting for 75–85% of tumors [4]. Other common types of RCC include papillary (10–15%) and chromophobe renal cell carcinomas (5%). In less than 5%, they are considered “unclassified renal cell carcinoma” and consist of transitional cell carcinoma, nephroblastoma or Wilms’ tumor, collecting duct tumor, renal sarcomas and renal medullary carcinoma [5].

Sixty-five percent of patients with renal cell carcinoma are staged as localized disease at initial presentation and are candidates for partial or radical nephrectomy with curative intent. Thirty percent of these patients with a diagnosis of localized disease will present distant recurrence. However, 15–30% of the patients are metastatic at diagnosis, and potential candidates for systemic treatment [2].

The knowledge of the lack of efficacy of cytotoxic chemotherapy and the understanding of the molecular pathogenesis of RCC – especially the clear cell subtype combined with the recognition of VEGF and the immunological pathways, altered the natural history of this disease, allowing the emergence of new therapeutic tools [6, 7].

## 27.2 Epidemiology

Worldwide, kidney cancer is the ninth most common malignant neoplasm, with more than 210,000 new cases diagnosed, and 91,000 deaths in 2012 [8]. Greater incidence is observed in the Czech Republic and North America [9]. In the United

States, there are approximately 65,000 new cases and nearly 15,000 RCC deaths each year. In the European Union, there were approximately 84,000 cases of RCC and 35,000 deaths from renal cancer in 2012 [10, 11].

Incidence rates have increased in most populations, but mortality rates have stabilized or decreased since the 1990s [12]. Early detection of tumors, especially smaller than 4 cm and improvement on systemic treatment, have contributed to the improvement of the survival in 5 years [13].

Men and women are affected in a ratio of 2:1 [14]. According to SEER data, it occurs predominantly between the sixth and the eighth decade of life, with a median age of presentation at 64 years old [15].

Environmental, hormonal, cellular and genetic factors have been studied as possible causal factors in the development of renal carcinoma. Smoking is considered the main risk factor, which is directly responsible for 30% of cases in men and 24% in women [16]. Obesity is associated with an increased risk of clear cell renal carcinoma, particularly in women [17]. Hypertension predisposes to the development of RCC, which appears to be independent of antihypertensive drugs or obesity [18]. Another risk factor is nephropathy due to abuse of analgesic, especially those containing phenacetin [19].

It is estimated that 5.8% of patients with acquired renal cystic disease (which affects 35–47% of patients with long-term renal dialysis) develop RCC and correspond to a risk 30 times higher than the general population [20].

Family history is also associated with an increased risk of renal cancer in both men and women [21].

### 27.3 Molecular Mechanisms of Clear Cell Renal Carcinoma

The VHL tumor suppressor gene, initially described in the Von Hippel-Lindau autosomal dominant syndrome, is located on chromosome 3p25 and predisposes to the development of clear cell renal carcinoma, central nervous system hemangioblastomas, retinal angiomas and pheochromocytoma. Inactivation of VHL tumor suppressor gene in sporadic, non-inherited clear cell carcinomas can occur by suppression of the VHL gene allele (84–98% of cases), mutations in the remaining allele (34–57% of cases), and of gene silencing by methylation [22].

The VHL gene product (pVHL) is a protein component that mediates the cellular response to hypoxia. Under normal oxygenation conditions, the VHL gene product (pVHL) binds and degrades the Inducible Hypoxia Factor (HIF) 1 $\alpha$  and 2 $\alpha$ . In situations of hypoxia or defective function of the VHL gene and protein, HIF is not destroyed and accumulates, leading to the transcription of hypoxia-inducible genes; production of VEGF and PDGF- $\beta$ ; tumor progression through cyclin D1 dysregulation and tumor promotion [23].

CCR frequently exhibits changes in the mTOR complex, which integrates oncogenic signals of cell proliferation and survival [24, 25].

It is believed that resection of the primary tumor of the kidney (RCC) can provoke an immune response that occasionally results in spontaneous and dramatic remissions in metastases, particularly in the lung [26, 27]. This theory led to the exploration of antitumor activity among various cytokines such as IL- 2 and IFN $\alpha$ . However, after controversial efficacy with these interleukins, the concept of current immunotherapy is directed at checkpoint inhibitors such as PD-1 and CTLA-4, which are targets of therapy currently being explored in a number of neoplasms.

## 27.4 Diagnosis and Staging

### 27.4.1 Clinical Manifestations (Table 27.1)

Approximately 30% of patients with renal carcinoma have metastatic disease, 25% with locally advanced renal carcinoma, and 45% with localized disease. Patients with RCC can remain clinically asymptomatic until the disease becomes advanced, and only 9% patients present the classic triad of renal cell carcinoma (flank pain, hematuria and palpable abdominal renal mass) [28].

**Table 27.1** Clinical manifestations

Clinical manifestations	
Hematuria <sup>a</sup>	40%
Hypochromic or normochromic anemia <sup>b</sup>	29–88%
Cachexia, fatigue and weight loss <sup>c</sup>	33%
Fever <sup>c</sup>	20%
Hypercalcemia <sup>d</sup>	15%
Scrotal varicoceles <sup>e</sup>	11%
Non-metastatic hepatic dysfunction (Stauffer) <sup>f</sup>	7%
Polycythemia <sup>g</sup>	5%
Secondary amyloidosis <sup>h</sup>	3–5%

<sup>a</sup>Gibbons RP, Monte JE, Correa RJ Jr, Mason JT (1976) Manifestations of renal cell carcinoma. *Urology* 8:201

<sup>b</sup>Chisholm GD, Roy RR (1971) The systemic effects of malignant renal tumours. *Br J Urol* 43:687

<sup>c</sup>Gold PJ, Fefer A, Thompson JA (1996) Paraneoplastic manifestations of renal cell carcinoma. *Semin Urol Oncol* 14:216

<sup>d</sup>de la Mata J, Uy HL, Guise TA et al (1995) Interleukin-6 enhances hypercalcemia and bone resorption mediated by parathyroid hormone-related protein in vivo. *J Clin Invest* 95:2846

<sup>e</sup>Johnson CD, Dunnick NR, Cohan RH, Illescas FF (1987) Renal adenocarcinoma: CT staging of 100 tumors. *AJR Am J Roentgenol* 148:59

<sup>f</sup>Utz DC, Warren MM, Gregg JA et al (1970) Reversible hepatic dysfunction associated with hypernephroma. *Mayo Clin Proc* 45:161

<sup>g</sup>Iliopoulos O, Levy AP, Jiang C et al (1996) Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. *Proc Natl Acad Sci U S A* 93:10595

<sup>h</sup>Pras M, Franklin EC, Shibolet S, Frangione B (1982) Amyloidosis associated with renal cell carcinoma of the AA type. *Am J Med* 73:426

There are several sites of metastases in advanced renal cell carcinoma. However, it is known that 75% of the patients have lung metastases, 36% for soft tissues, 20% for bone, 18% for the liver, 8% for cutaneous sites and 8% for the central nervous system [29].

Hematuria is the most known of the warning signs for renal cancer occurring in 40% of patients, but is observed only when there is tumor invasion of the collecting system [30]. Palpable abdominal mass is associated with tumors of the lower pole of the kidney [31]. Hypochromic or normochromic anemia, observed in 29–88% of patients, may precede the diagnosis for several months and may occur due to hematuria or hemolysis. In addition, approximately 5% of patients with renal cancer have polycythemia [32, 33]. Other symptoms such as fever, of unknown origin, cachexia, fatigue and weight loss are observed between 20 and 33% [34].

Systemic complications such as hypercalcemia, secondary amyloidosis or hepatic dysfunction can be observed in 15%, 5% and 7%, respectively [7, 35, 36]. Less usual consequences such as left varicoceles can be observed in up to 11% of men with carcinoma of renal cells [37].

### **27.4.2 Diagnostic Evaluation**

After improving diagnostic methods, many patients have been diagnosed incidentally which has improved the survival of these patients. The diagnostic modalities used to evaluate renal mass lesions evolved from excretory urography to CT, USG and MRI.

The most common examination is CT, which allows the physician to detect small renal tumors with good sensitivity. Although USG is less sensitive than CT in detecting a renal mass, it is useful in distinguishing between a simple benign cyst and a more complex cyst or a solid tumor. Magnetic resonance imaging (MRI) may be useful when ultrasound and CT scan are not sufficient for diagnosis or when there is no indication for the use of radiographic contrast [38].

### **27.4.3 Systemic Staging**

In addition to history and physical examination, the following exams should be requested: complete blood count, metabolic profile (serum calcium, enzymes and liver function, alkaline phosphatase, urea, creatinine, electrolytes) and LDH. Systemic staging includes CT or MRI of the abdomen, chest tomography, bone scintigraphy, and brain MRI depending on clinical judgment [39]. Positron emission tomography (PET-CT) has controversial use in this neoplasm, with sensitivity varying between 60 and 90%, specificity of 91% and accuracy of 90%. This examination may be useful in selected cases, with doubtful lesions or in candidates for resection of metastases [40].

**Table 27.2** Risk criteria

Parameter	Classic Motzer criteria <sup>a</sup>	IMDC <sup>b</sup>
	Value	Value
Nephrectomy status	< 1 year	< 1 year
Karnofsky	< 80%	< 80%
DHL	>1.5 x NVL	*
Serum calcium (albumin-corrected)	>10	>10
Anemia	< NVL	< NVL
Neutrophilia	*	>NVL
Thrombocytosis	*	>NVL
	<b>Risk factors</b>	<b>Overall survival</b>
Low risk	no adverse prognostic factors present	43,2 months
Intermediate risk	1 or 2 risk factors	22,5 months
High risk	3 or more risk factors	7,8 months

<sup>a</sup>Motzer RJ et al (2002) Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 20(1):289–296

<sup>b</sup>Heng DYC et al (2009) Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. *J Clin Oncol* 27:5794

#### 27.4.4 Risk Stratification in Stage IV (Table 27.2)

Motzer criteria were established for patients who were treated primarily with interferon-alpha, although phase III study analysis with sunitinib versus interferon (IFN) validated these risk categories in subjects treated with sunitinib [41].

Another study of the IMDC database, which evaluated prognostic criteria in patients treated with anti-VEGF molecular target therapy, validated four of the five MSKCC criteria (time between diagnosis and treatment less than 1 year, KPS <80%, elevated serum calcium and presence of anemia) and added two more (neutrophilia and thrombocytosis) [42].

#### 27.4.5 TNM Staging (Tables 27.3 and 27.4)

The eighth TNM (2017) is used for the staging of all histological variants of renal cell carcinoma (RCC). Tumors limited to the kidney are classified as T1 or T2 based on size. T3 tumors extend into the renal vein or perirenal tissues, but not beyond the Gerota's fascia. T4 tumors have as main characteristic their extension beyond the Gerota's fascia, including the direct extension to the ipsilateral adrenal gland. Nodal and distal metastases are simply classified as absent or present [43].

**Table 27.3** Staging TNM<sup>a</sup>

Primary tumor (T)	
T category	T criteria
<b>TX</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>T1</b>	Tumor ≤7 cm in greatest dimension, limited to the kidney
<b>T1a</b>	Tumor ≤4 cm in greatest dimension, limited to the kidney
<b>T1b</b>	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
<b>T2</b>	Tumor >7 cm in greatest dimension, limited to the kidney
<b>T2a</b>	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
<b>T2b</b>	Tumor >10 cm, limited to the kidney
<b>T3</b>	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota’s fascia
<b>T3a</b>	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota’s fascia
<b>T3b</b>	Tumor extends into the vena cava below the diaphragm
<b>T3c</b>	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
<b>T4</b>	Tumor invades beyond Gerota’s fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)	
N category	N criteria
<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M category	M criteria
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis

<sup>a</sup>AJCC (2017) Cancer staging manual, 8th edn. Ed. Springer

**Table 27.4** Grouping and prognosis<sup>a</sup>

Staging	T	N	M	Survival (5y)
<b>I</b>	T1	N0	M0	96%
<b>II</b>	T2	N0	M0	82%
<b>III</b>	T1 or T2 T3	N1 N0	M0	64%
<b>IV</b>	T4 TX	NX NX	M0 M1	23%

<sup>a</sup>AJCC (2017) Cancer staging manual, 8th edn. Ed. Springer

### 27.4.6 Screening

There is no evidence-based recommendation for renal cell cancer screening in the general population, given its low prevalence [44]. In patients at risk for renal cancer (kidney transplant recipients, dialytics, or individuals who are members of families with any of the hereditary renal cancer syndromes) must have individualized conduct, since there is also no validated guideline in these situations.

## 27.5 Patology – Histology Subtypes (Table 27.5)

**Clear cell carcinomas:** arise from the proximal tubule and usually have a deletion of chromosome 3p, where the VHL gene is located. This gene is related to VHL syndrome and the sporadic form of clear cell carcinoma. Macroscopically, they may be solid or less commonly cystic. The presence of a higher nuclear grade or the presence of a sarcomatoid pattern confer a worse prognosis. Although mutations in the p53 gene are identified infrequently in CCRs, overexpression of the p53 protein is detected in approximately half of the tumors and is associated with more aggressive behavior and worse prognosis [8, 45, 46].

**Papillary carcinomas:** arise from the proximal tubule and account for approximately 15% of all renal cancers. Type 1 papillary RCC generally presents in early stages and has a favorable prognosis. In the hereditary form, activating germ mutations are found in the MET. In sporadic forms, somatic mutations in MET are found in 10–20% of cases. Tumors classified as papillary type 2 RCC are associated with more aggressive forms, usually stages III or IV at diagnosis. These tumors have also been observed in hereditary leiomyomatosis and renal cell cancer syndrome, caused by germ mutation in the Hereditary Fibromatosis gene [47].

**Chromophobe carcinomas:** they originate from the intercalated cells of the collecting ducts. Histologically, chromophobe carcinomas are composed of a darker cell pattern than clear cell carcinoma. They usually have a lower risk of disease progression and death compared to clear cell carcinomas, although the diagnosis of these patients occurs more frequently in the early stages [48, 49].

**Oncocytomas:** originate from the intercalated cells of the collecting ducts. They represent 3–7% of all renal tumors and consist of a pure population of oncocytes, which are large and well differentiated neoplastic cells with intensely eosinophilic granular cytoplasm due to a large number of mitochondria. While sporadic tumors are usually unilateral and unique, multiple and bilateral oncocytomas have been described in patients with tuberous sclerosis complex (TSC) and Birt-Hogg-Dubé syndrome. Renal oncocytomas behave benignly and even when very large, they are generally well encapsulated and are rarely invasive or associated with metastases [50].

**Collector duct tumors:** rare tumors, more frequent in black patients. They are usually diagnosed with more advanced disease (T3/T4) or metastatic disease and tend to occur in younger patients. They are often aggressive and usually with macroscopic hematuria [51].

**Renal medullary carcinoma:** highly aggressive neoplasia, found in young, black, male patients with sickle cell trait and, less commonly, sickle cell disease. Patients usually complain of macroscopic hematuria, urinary tract infection, flank pain, abdominal mass and or weight loss. Metastatic disease is commonly present at diagnosis and the prognosis is poor, with an expected survival of 6–12 months [52, 53].

**Translocation carcinoma:** tends to occur in younger patients compared to other RCCs. Their presence has been shown in children who have received previous

**Table 27.5** Histology subtypes

Histological subtype	%	Genetic / chromosomal alteration	Source	Observação
Clear cell carcinoma <sup>a</sup>	75–85%	Deletion chromosome 3p / VHL gene mutation	Proximal tubule	
Carcinoma of papillary cells <sup>b</sup>	10–15%	Trisomy of 16, 17 and 20. Mutation	Proximal tubule	Type 1: low grade and better prognosis
Chromophobic cell carcinoma <sup>c</sup>	5–10%	Hypoploidy with loss of several chromosomes. BHD gene mutation	Collector duct	Type 2: high grade and worse prognosis
Carcinoma of duct collector <sup>d</sup>	Rare		Collector duct	
Medullary carcinoma <sup>e</sup>	Rare		Collector duct	
Oncocitoma <sup>f</sup>	Unusual	Rearrangement 11q13	Collector duct	Aggressive disease with pathological features similar to the transitional cell tumor.
Translocation Carcinoma Xp11.2 2	Rare	Fusion of the TFE3 gene with the ASPL and PRCC genes		A type of collecting duct carcinoma that occurs in patients with sickle cell anemia.

<sup>a</sup>Bielsa O, Lloreta J, Gelabert-Mas A (1998) Cystic renal cell carcinoma: pathological features, survival and implications for treatment. *Br J Urol* 82:16

<sup>b</sup>Cancer Genome Atlas Research Network, Linehan WM, Spellman PT et al (2016) Comprehensive molecular characterization of papillary renal-cell carcinoma. *N Engl J Med* 374:135

<sup>c</sup>Thoenes W, Störkel S, Rumpelt HJ et al (1988) Chromophobe cell renal carcinoma and its variants – a report on 32 cases. *J Pathol* 155:277

<sup>d</sup>Orsola A, Trias I, Raventós CX et al (2005) Renal collecting (Bellini) duct carcinoma displays similar characteristics to upper tract urothelial cell carcinoma. *Urology* 65:49

<sup>e</sup>Swartz MA, Karth J, Schneider DT et al (2002) Renal medullary carcinoma: clinical, pathologic, immunohistochemical, and genetic analysis with pathogenetic implications. *Urology* 60:1083

<sup>f</sup>Speicher MR, Schoell B, du Manoir S et al (1994) Specific loss of chromosomes 1, 2, 6, 10, 13, 17, and 21 in chromophobe renal cell carcinomas revealed by comparative genomic hybridization. *Am J Pathol* 145:356

chemotherapy for other malignancies, autoimmune disorders or bone marrow transplantation conditioning. A distinct variant of CRC, referred to as translocation carcinoma, is associated with the fusion of the TFE3 gene with several other genes, including ASPL and PRCC on chromosome Xp11.2 [54].

**Hereditary syndrome (summarized in Table 27.6)**



**Table 27.6** Hereditary syndromes related to increased incidence of renal cancer

Syndrome	Mutation	Tumor subtypes
Von Hippel-Lindau <sup>a</sup>	Tumor suppressor gene VHL (chromosome 3)	Clear Cell Renal Cancer Cerebral or retinal or spinal cord hemangioblastoma Adrenal cancer
Hereditary papillary renal carcinoma <sup>b</sup>	Proto-oncogene MET (Chromosome 7)	Pure papillary carcinoma, often multicentric Type 1: low grade and best prognosis Type 2: high grade Chromophobe renal cell carcinoma
Birt-Hogg-Dubé <sup>c</sup>	BHD1 Gene(Chromosome 17)	Oncocytic tumors / oncocytomas Benign skin tumors Pulmonary cysts (frequent cause of spontaneous pneumothorax)
Familial leiomyomatosis <sup>b</sup>	Fumarate hydratase (chromosome 1)	Aggressive type renal papillary carcinoma Benign skin tumors Uterine leiomyomas

<sup>a</sup>Beroukhim R, Brunet JP, Di Napoli A et al (2009) Patterns of gene expression and copy-number alterations in von-hippel lindau disease-associated and sporadic clear cell carcinoma of the kidney. *Cancer Res* 69:4674

<sup>b</sup>Vera Badillo FE et al (2015) Systemic therapy for non-clear cell renal cell carcinomas: a systematic review and meta-analysis. *Eur Urol* 67:740–749

<sup>c</sup>Störkel S, Steart PV, Drenckhahn D, Thoenes W (1989) The human chromophobe cell renal carcinoma: its probable relation to intercalated cells of the collecting duct. *Virchows Arch B Cell Pathol Incl Mol Pathol* 56:237

## 27.6 Treatment

### 27.6.1 Localized Regional Disease Treatment (Table 27.7)

#### Watchful Watching

Patients with high surgical risk or reduced life expectancy, watchful watching is an option, especially for small tumors and low risk of Motzer criteria. This option for no treatment is based on the observation that the growth rate in general of renal parenchymal tumors varies from 0.28 to 0.34 cm per year for tumors up to 4 cm and 0.57 with per year for tumors above 4 cm. In highly selected patients with informed risks of this approach, watchful watching may be considered an important option [55].

#### General Surgical Principles

Definitive surgical treatment for renal cell carcinoma encompasses either partial or radical nephrectomy. Factors such as tumor location, presence of multiple or bilateral tumors, single kidney or impairment of contralateral renal function, and history of a hereditary renal cancer syndrome may be important in choosing one approach or another.

**Table 27.7** Locoregional treatments and indications

Locoregional treatments	Indications
<b>Radical nephrectomy</b> <sup>a</sup>	- Tumors > 7 cm in size  - Any of the following: <ul style="list-style-type: none"> <li>• Central tumors</li> <li>• Suspected involvement of retroperitoneal lymph nodes</li> <li>• Renal vein involvement or associated inferior vena cava</li> <li>• Direct invasion of the ipsilateral adrenal gland</li> </ul>
<b>Partial Nephrectomy</b> <sup>a</sup>	- Tumors ≤ 7 cm  - Any of the following: <ul style="list-style-type: none"> <li>• Single kidney</li> <li>• Multiple, small and / or bilateral tumors</li> <li>• Patients with established chronic kidney disease</li> </ul>
<b>Ablative techniques or enucleation</b> <sup>b</sup>	- Option in tumors ≤ 4 cm (T1a), representing another option to consider, especially in cases of high surgical risk or that decline to partial or radical nephrectomy.

<sup>a</sup>Krabbe LM, Bagrodia A et al (2014) Surgical management of renal cell carcinoma. *Semin Intervent Radiol* 31(1):27–32

<sup>b</sup>Kunkle DA, Uzzo RG (2008) Cryoablation or radiofrequency ablation of the small renal mass: a meta-analysis. *Cancer* 113:2671

**Radical Nephrectomy**

Radical nephrectomy (open, laparoscopic or robotic) consists of ligation of the renal artery and vein, removal of the kidney and fascia from Gerota, and occasionally from the ipsilateral adrenal gland. However, in the absence of high risk of local adrenal gland invasion, resection of the adrenal gland should be omitted because of the low incidence of metastases to these glands (10% or less). Retroperitoneal lymphadenectomy should be performed in patients with suspected retroperitoneal involvement, grade 3 or 4 tumor, sarcomatoid histology and presence of coagulative necrosis [56].

In patients with renal cell carcinoma limited to the kidney, a radical nephrectomy results in a 5-year specific cancer survival rate between 80 and 93%, regardless of the technique used [57].

**Partial Nephrectomy**

Treatment indicated for smaller tumors with a greater possibility of preserving renal function. A retrospective series including 7138 patients compared the difference in overall survival of those individuals who underwent partial (27%) vs. radical nephrectomy (73%) at a follow-up of 62 months. Individuals treated with partial nephrectomy had a lower overall risk of death (HR = 0.54, 95% CI: 0.34–0.85), but similar cancer-specific survival rates [58].

### **Alternative Approaches**

For patients who are not candidates for surgery for any reason, nephron sparing approaches such as enucleation and thermal ablation (radiofrequency ablation or cryotherapy) are appropriate alternatives.

Enucleation consists of removal of the tumor without dissection in the non-involved renal parenchyma. Although limited non-prospective data suggest that it is comparable to surgery for treating small renal lesions, nephrectomy is still the standard treatment. In a series of more than 200 patients with a tumor <4 cm (median of 2.9 cm) treated with enucleation, the 10-year cancer-specific cancer survival rate was 95% [59].

Local ablative therapies are minimally invasive guided imaging procedures. Cryoablation or radiofrequency has shown excellent results in tumors  $\leq 4$  cm (T1a) and represent another treatment option, especially in cases of high surgical risk or that decline to partial or radical nephrectomy [60]. They may also be a therapeutic option for patients with syndromes related to multiple renal tumors and as salvage therapy for recurrences (new nodules or relapses in a surgical site).

## **27.6.2 Role of Surgery in Metastatic Disease**

The treatment of choice for patients with advanced renal disease is based on systemic therapy, usually involving immunotherapy or agents directed to the VEGF pathways. However, due to the indolent growth of renal tumors, treatment options such as resection of oligometastases or nephrectomy have become recognized treatment options.

### **27.6.2.1 Palliative Nephrectomy**

Two randomized studies have shown that nephrectomy increases the survival of patients treated with interferon, even when the disease is in stage IV. The SWOG study, which randomized 246 patients with metastatic RCC for interferon alpha alone versus nephrectomy followed by the same systemic treatment, demonstrated benefit in OS with nephrectomy (11 versus 8 months;  $p$ : 0.05) [61]. The EORTC study randomized 83 patients for the same strategy and demonstrated benefit in PFS (5 versus 3 months,  $p$  < 0.05) and OS (17 versus 7 months,  $p$  < 0.05) for the patients operated on in this setting [62].

However, these data are not supported by the CARMENA study which included 450 patients with metastatic clear cell renal cell carcinoma at diagnosis and demonstrated that in patients at intermediate and high risk the isolated sunitinib was not inferior to cytoreductive nephrectomy followed by sunitinib in terms of OS (18.4 versus 13.9 months, HR: 0.89, upper limit of the 95% confidence interval for non-inferiority,  $\leq 1.20$ ). In view of these findings, the indication of cytoreductive nephrectomy in the metastatic scenario should be considered an exception [63].

It remains unanswered, what would be the role of cytoreductive nephrectomy in the era of immunotherapy. Palliative nephrectomy may be an important resource in symptomatic patients with pain or hematuria [64].

### 27.6.2.2 Metastasectomy

Resection of distant metastasis, mostly in patients with clear cell carcinoma, appears to have a favorable impact on the treatment of metastatic kidney cancer. Complete surgical resection of isolated lung metastases in carefully selected patients has been associated with a 5-year survival of 20–50% [65]. Excision of bone metastases may be considered in carefully selected patients for pain relief and tumor control with survival improvement at one and 5 years of 47% and 11%, respectively [66]. Despite the negative impact of liver metastases on survival, resections of solitary metachronous liver metastases are possible, with survival in 2 years greater than 50% in selected patients [66]. In addition, resection of the residual disease after systemic therapy may present a favorable survival result [67].

## 27.7 Systemic Treatments

### 27.7.1 Adjuvant Treatment

Recently, three large studies have generated conflicting results regarding the role of adjuvant treatment in post-nephrectomy kidney cancer and with high-risk characteristics.

**Sunitinib:** The ASSURE trial randomized 1943 patients considered high risk (T1b and high grade; T4, any grade, and any N) after nephrectomy to receive sunitinib, sorafenib or placebo. Interim analysis didn't demonstrate statistically significant differences between the three groups in PFS and OS [68]. On the other hand, the S-TRAC study recruited 615 patients at higher risk (stage pT  $\geq$  3, presence of lymph node metastases, or both) to receive sunitinib or placebo, and observed a statistically significant gain of 1.2 years for PFS (6.8 versus 5.6 years, HR = 0.76, p = 0.03). The OS data are still immature and the median has not yet been reached (HR = 0.92, p = 0.6) [55]. It is important to note that the ASSURE study recruited a population with a lower risk than S-TRAC trial, justifying the differences in PFS results.

**Pazopanib:** The PROTECT study also evaluated the use of adjuvant pazopanib in patients with high-grade stage T2 or  $\geq$  T3, including N1, clear cell renal carcinoma. Pazopanib, 600 mg failed to demonstrate an increase in PFS (HR = 0.86, p = 0.165) [69].

In light of all controversy, whether or not to decide adjuvant treatment for kidney cancer will depend on patient adherence to treatment and associated adverse events. The decision must be made in an individualized way, since there is no OS benefit.

## 27.7.2 Systemic Treatment of Metastatic Disease Renal Cell Carcinoma Histology (Tables 27.8 and 27.10)

### 27.7.2.1 Antiangiogenic Therapy and Target-Targeted Therapy

**Pazopanib:** Phase III study, with 435 patients with clear-cell renal cell carcinoma with good and intermediate risk, treatment-naïve or second-line after cytokines, demonstrated a statistically significant benefit pazopanib treatment versus placebo in median PFS (9 versus 4 months, HR: 0.46,  $p < 0.05$ ). The loss of benefit in OS was possibly attributed to a high rate of cross over and the use of other treatments after disease progression in the placebo arm [70].

**Sunitinib:** A phase III study of 750 patients with clear-cell renal carcinoma with good or intermediate risk, treatment-naïve, demonstrated a statistically significant gain with sunitinib (50 mg for 4 weeks, 2 weeks off) versus interferon-alpha at a rate of ( $p < 0.05$ ) and mean OS (26.4 versus 21.8 months, HR 0.82,  $p < 0.05$ ) [71].

**Pazopanib versus sunitinib:** O The COMPARZ study involved 1100 patients and demonstrated non-inferiority of pazopanib versus sunitinib in median PFS (8.4 versus 9.5 months; HR = 1.04; 95% CI: 0.09–1.22) and OS (28.4 versus 29.3 months, HR = 0.90, 95% CI 0.76–1.08), with a toxicity profile (except elevation of transaminases/bilirubins) and quality of life analysis favoring pazopanib [72]. The PISCES study favored pazopanib's preference for sunitinib between the patients (70% versus 22%) and physicians (61% versus 22%) [73].

**Cabozantinib:** The METEOR trial, which randomized 658 patients with at least one prior treatment line with VEGF inhibitor, demonstrated gains of cabozantinib over everolimus in median PFS (7.4 versus 3.9 months, HR = 0.51,  $p < 0.001$ ), objective response (17 versus 3%,  $p < 0.001$ ) and median OS (21.4 versus 16.5 months; HR = 0.66, 95% CI 0.53–0.83,  $p = 0.00026$ ). The toxicity profile was different between the two arms, with a higher incidence of diarrhea, fatigue, hand-foot syndrome and hypertension for cabozantinib, and a higher incidence of anemia, cutaneous rash, dyslipidemia, hyperglycemia and pneumonitis in everolimus's arm [74]. The phase study II CABOSUN, randomized 157 patients at intermediate or high risk, and showed a benefit with cabozantinib over sunitinib in median PFS (8.2 versus 5.6 months; HR = 0.66;  $p = 0.012$ ) [75].

**Axitinib:** The AXIS trial randomized 723 patients and demonstrated a greater efficacy of axitinib over sorafenib in median PFS (8 versus 6 months, HR 0.66,  $p < 0.05$ ), but with any median OS benefit (20 versus 19 months, HR 0.96, 95% CI % 0.80–1.17). In the first-line setting, in a multicenter study in 288 patients, axitinib compared to sorafenib did not show benefit in PFS (10 versus 6.5 months, HR 0.77, 95% CI 0.56–1.05) or OS (21.7 vs 23.3 months, HR 0.995, 95% CI 0.31–1.36) [76].

**Table 27.8** Clear Cell kidney cancer treatments options

	1st line	2nd line	3rd line
<b>Clear cell</b>			
<b>Good prognosis (MSKCC)</b>	Pazopanib (preference) <sup>a</sup> Sunitinib <sup>b</sup> Bevacizumab + Interferon <sup>c</sup>	Nivolumab (preference) <sup>d</sup> Cabozantinib <sup>e</sup> Lenvatinib + Everolimus <sup>f</sup> Axitinib <sup>g</sup>	Everolimus or not previous used VEGF inhibitor <sup>h</sup>
<b>Intermediate or unfavorable prognosis (MSKCC)</b>	Nivolumab + Ipilimumab (preference) <sup>i</sup> Cabozantinib <sup>j</sup> Pazopanib <sup>a</sup>	Pazopanib <sup>a</sup> Sunitinib <sup>k</sup> Axitinib <sup>g</sup> Cabozantinib <sup>e</sup>	Everolimus or not previous used VEGF inhibitor <sup>h</sup>

<sup>a</sup>Motzer RJ, Hutson TE, McCann L et al (2014) Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med* 370:1769

<sup>b</sup>Motzer RJ, Hutson TE, Tomczak P et al (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 27:3584

<sup>c</sup>Bracarda S, Bellmunt J, Melichar B et al (2011) Overall survival in patients with metastatic renal cell carcinoma initially treated with bevacizumab plus interferon- $\alpha$ 2a and subsequent therapy with tyrosine kinase inhibitors: a retrospective analysis of the phase III AVOREN trial. *BJU Int* 107:214

<sup>d</sup>Escudier B, Motzer RJ, Sharma P et al (2017) Treatment beyond progression in patients with advanced renal cell carcinoma treated with Nivolumab in CheckMate 025. *Eur Urol* 72:368

<sup>e</sup>Choueiri TK, Escudier B, Powles T et al (2015) Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 373:1814

<sup>f</sup>Motzer RJ, Hutson TE, Glen H et al (2015) Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol* 16:1473

<sup>g</sup>Rini BI, Escudier B, Tomczak P et al (2011) Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 378:1931

<sup>h</sup>Motzer RJ, Barrios CH, Kim TM et al (2013) Record-3: phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 31(suppl):abstr 4504

<sup>i</sup>Motzer RJ, Tannir NM, McDermott DF et al (2018) Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 378:1277

<sup>j</sup>Choueiri TK, Halabi S, Sanford BL et al (2017) Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol* 35:591

<sup>k</sup>Escudier B, Eisen T, Stadler WM et al (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 356:125–134

**Bevacizumab:** The role of bevacizumab in metastatic kidney cancer was demonstrated in The Avoren and CALGB 90206 trials. IFN plus bevacizumab was compared to IFN alone in both randomizations. The first study showed a superiority PFS to combination arm (10.2 versus 5.4 months; HR = 0.63;  $p = 0.0001$ ); The CALGB 90206 demonstrated better PFS with 8.4 versus 4.9 months favoring experimental arm; HR = 0.71;  $p < 0.0001$ ) [77, 78].

### 27.7.2.2 mTOR Inhibitors

**Temsirolimus:** A randomized study with 626 patients and predominantly poor risk metastatic renal carcinoma, demonstrated overall survival superiority (10.9 versus 7.3 months; HR = 0.73,  $p = 0.008$ ) of temsirolimus versus IFN [79].

**Everolimus:** The phase II study RECORD-3 randomized 471 patients to receive initial treatment with everolimus followed by sunitinib until progression versus sunitinib followed by everolimus to progression. The study failed to demonstrate non-inferiority of everolimus in the first line compared to sunitinib. Median OS was 22.4 months (95% CI 18.6–33.3) for everolimus-sunitinib and 29.5 months (95% CI 22.8–33.1) for sunitinib-everolimus (HREVE-SUN/SUN-EVE, 1.1; 95% CI 0.9–1.4). This analysis support the sequence of sunitinib followed by everolimus at progression in patients with mRCC [80, 81].

### 27.7.2.3 Immunotherapy

**Nivolumab:** The CheckMate-025 study randomized 821 patients for which they had received previous treatment with one or two regimens of antiangiogenic therapy were randomly assigned to receive Nivolumab or Everolimus. The Nivolumab arm demonstrated statistically benefit in median overall survival (25 versus 19.6 months; HR = 0.73;  $p = 0.018$ ). Additionally, nivolumab was better tolerated, with a lower incidence of adverse events grade  $\geq 3$  and better quality of life scores throughout the treatment. The expression of PD-L1 as a predictive factor of response was also evaluated, but there was no difference in the benefit of nivolumab among patients with PD-L1  $\geq 1$  or  $< 1\%$  expression [82].

**Nivolumab + Ipilimumab:** The CheckMate 214 trial demonstrated the benefit of the combination of ipilimumab and nivolumab versus sunitinib in the intermediate and unfavorable risk population. For patients with intermediate or unfavorable risk disease and tumor PD-L1 expression  $\geq 1\%$  ( $n = 214$ ), the combination arm showed superior response rate (58% versus 25%) and better median PFS (22.8 versus 5.9 months, HR 0.48,  $p < 0.05$ ). The same benefit was demonstrated with overall survival, that was significantly increased (median not achieved for both groups, HR 0.73, 95% CI, 56–0.96). However, when assessing only the favorable risk population ( $n = 249$ ), sunitinib alone was superior to the combination. The overall response rate was 52 versus 29% to sunitinib versus experimental arm, respectively, with  $p = 0.0002$  as well as with PFS (25.1 versus 15.3 months, HR = 2.18, 95% CI: 1.29–3.68,  $p < 0.0001$ ) [83].

**Atezolizumab + Bevacizumab:** The Phase III study, IMmotion151, randomized 1277 patients with metastatic kidney cancer to receive first-line combination of atezolizumab + bevacizumab or sunitinib. The patients were stratified into positive or negative PD-L1 (characterized as  $\geq 1\%$  or  $< 1\%$  expression in tumor cells, respectively). The study was discontinued because it reached its efficacy endpoint, and the interim analysis showed a statistically superiority in PFS (11.2 versus 8.4 months) for the combination arm (HR 0, 83, 95% CI 0.70–0.97,

$p = 0.0219$ ), and better results in PD-L1 positive population (HR 0.74, 95% CI 0.57–0.96,  $p = 0.0217$ ). In overall survival data, the both primary endpoints of the study are still immature in the present analysis [84].

**Interleukin-2:** The use of high-dose IL-2 therapy is no longer the standard choice, especially with the advent of VEGF inhibitors and new immunotherapy, mainly checkpoint inhibitors, drugs with fewer toxicities, and promising results. However, it is considered that even today, IL-2 may be an option for selected patients. In a combined analysis of 259 patients, 30 partial responses (12%) and 23 complete responses (9%) were seen. Among patients who had a complete response, 19 of 23 (83%) remained free of recurrence at the last follow-up. Results from several large randomized studies subsequently corroborate these results [85].

### 27.7.3 Systemic Treatment of Non-clear Cell Kidney Cancer (Table 27.9)

**Papillary carcinoma of the renal cell:** Resistant to several kinds of systemic treatments.

**Sunitinib:** The ASPEN trial recruited 108 non-clear cell kidney cancer patients (metastatic papillary, chromophobe, or unclassified non-clear cell renal cell carcinoma – 65% with papillary carcinoma). Sunitinib significantly increased progression-free survival compared with everolimus (8.3 months [80% CI 5.8–11.4] vs 5.6 months [5.5–6.0]; hazard ratio 1.41 [80% CI 1.03–1.92];  $p = 0.16$ ), although heterogeneity of the treatment effect was noted on the basis of histological subtypes and prognostic risk groups. Subgroup analysis has shown that patients with papillary tumors had better PFS with sunitinib than everolimus (8.1 months vs 5.5 months). Overall survival was not different between the two treatment groups (HR 1.12 [95% CI 0.7–2.1];  $p = 0.60$  [86]).

- (a) **Everolimus:** The phase II RAPTOR study included 92 patients with papillary carcinoma types I and II to receive everolimus 10 mg/day and demonstrated a 4.1 months progression free survival, stable disease in 65% of subjects and median OS with 21.4 months [87].
- (b) **Bevacizumab + Erlotinib:** The phase II study presented at the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, involved 41 patients with papillary carcinoma (20 with advanced hereditary leiomyomatosis and renal cell cancer and 21 with advanced sporadic papillary renal cell carcinoma). Patients received bevacizumab 10 mg/kg given intravenously once every 2 weeks, combined with erlotinib 150 mg taken orally every day. The median progression-free survival in the hereditary leiomyomatosis and renal cell cancer cohort was 24.2 months, while for sporadic papillary renal cell carcinoma cohort it was 7.4 months. The overall response rate was 65% [88].



**Table 27.9** Non-clear cell carcinoma treatment options

1st line	
<b>Papillary carcinoma</b>	Sunitinib 4:2 <sup>a</sup> Sunitinib 2:1 <sup>a</sup> Bevacizumab + Erlotinib <sup>b</sup> Or Tensirolimus or Everolimus <sup>c</sup>
<b>Carcinoma with sarcomatoid components</b>	Sarcomatoid components $\geq 20\%$ : Sunitinib + gemcitabine <sup>d</sup> Sarcomatoid components $<20\%$ : Sunitinib or Pazopanib or Bevacizumab <sup>c</sup>
<b>Chromophobic cell carcinoma</b>	Sunitinib 4:2 <sup>f</sup> Sunitinib 2:1 <sup>f</sup> Sorafenib <sup>f</sup> Or Tensirolimus or Everolimus <sup>c</sup>
<b>Carcinoma of the collecting duct</b>	Cisplatin or Carboplatin + Gemcitabine <sup>g</sup>
<b>Renal medullary carcinoma</b>	MVAC dose dense <sup>h</sup> Cisplatin + Gemcitabine <sup>h</sup>
<b>Renal Carcinoma with Translocation Xp11.2 (TFE3)</b>	Treat like clear cell carcinoma

<sup>a</sup>Armstrong AJ, Halabi S, Eisen T et al (2016) Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol*

<sup>b</sup>Srinivasan R et al (2014) Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib (abstract 5). In: EORTC-NCI-AACR symposium on molecular targets and cancer therapeutics

<sup>c</sup>Hudes G, Carducci M, Tomczak P et al (2007) Tensirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 356:2271

<sup>d</sup>Michaelson MD, McDermott DF, Atkins MB et al (2013) Combination of antiangiogenic therapy and cytotoxic chemotherapy for sarcomatoid renal cell carcinoma. *ASCO Meeting Abstracts* 31:4512

<sup>e</sup>Golshayan AR, George S, Heng DY et al (2009) Metastatic sarcomatoid renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *J Clin Oncol* 27:235

<sup>f</sup>Choueiri TK, Plantade A, Elson P et al (2008) Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol* 26:127

<sup>g</sup>Oudard S, Banu E, Vieillefond A et al (2007) Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Génitales) study. *J Urol* 177:1698

<sup>h</sup>Carlos MI et al (2016) Medullary renal cell carcinoma (RCC): Genomics and treatment outcomes. *J Clin Oncol* 34:4556

## Carcinoma with Sarcomatoid Component

**A. Sunitinib + Gemcitabine:** A phase II study including 35 patients evaluated the combination of sunitinib and gemcitabine in subjects with sarcomatoid component, observing efficacy apparently superior to historical data, with a 30% ORR, a total clinical benefit of 60%, a median PFS of 3.5 months and median OS of 11 months representing another option in patients with sarcomatoid component  $\geq 20\%$  [89].

**B. Sunitinib, sorafenib or bevacizumab:** in a retrospective study involving 43 patients there were no significant responses in individuals with this sarcomatoid component  $\geq 20\%$ . On the other hand, in patients with less than 20% sarcomatoid component the objective response rate was 33% ( $p = 0.02$ ) [90].

**Chromophobe cell carcinoma:** Although there was scant literature on the efficacy of anti-VEGF agents in chromophobe cell carcinomas, a study involving 53 patients with chromophobe carcinoma, ORR to sunitinib or sorafenib was 23%; Median PFS was 10.6 months [91]. The Aspen trial included 16% of chromophobe carcinoma. The exploratory analysis showed that everolimus was associated with a longer median progression-free survival than that of sunitinib. Although the study were unable to test for treatment group by subgroup interactions, the differences in median progression-free survival are clinically important and warrant further confirmation and reporting in larger trials [86].

**Collecting duct carcinoma (Bellini's duct):** Carcinoma of the collecting ducts of Bellini (CDC) is a rare and aggressive renal disease. This tumor derives from the distal nephron and arises from the epithelial layer of distal tubules, which is more similar to the urothelial cells than to renal cells [92]. A phase II study with cisplatin or carboplatin and gemcitabine included 23 patients with renal collecting duct carcinoma and demonstrated an 26% ORR and 10.5 months OS [93]. A retrospective analysis with 13 patients treated with anti VEGF antibodies showed that the overall disease control in the CDC population was 23%, and median overall survival was 4 (95% confidence interval(CI) = 2.4–5.6) months. Three patients obtained a satisfying response (disease control lasting 6–33 months) [94].

**Renal Medullary Carcinoma:** There are few data about the treatment of this rare neoplasm, but chemotherapy is usually given in the first line. One of the main features of this rare tumor is the loss of expression of SMARCB1, a chromatin remodeling gene present in 100% of cases according to study including 23 patients that contained sample for analysis. In this study, including 32 subjects, the OS and PFS were 5.8 and 2.9 months, respectively, and the ORR was 36% in 11 patients treated with platinum-based regimens [95, 96].

**Renal Carcinoma with Translocation Xp11.2 (TFE3):** This is another rare neoplasm with almost none information about its treatment. One study reported results from a series of 15 patients who received VEGF-targeted therapies (sunitinib, sorafenib and bevacizumab); 5 of the 15 patients received previous systemic therapy. The median PFS was 7.1 months and the median OS was 14.1 months [97].

### 27.7.3.1 Immunotherapy in Non-clear Cell Renal Carcinoma (Tables 27.10 and 27.11)

Clinical trials with nivolumab excluded those patients whose tumors did not have clear cell components. In the largest series of cases with 35 patients included in this scenario, under median follow-up of 8.5 months, there were 7 partial responses (20%) and 10 had a stable disease (29%) [98].

**Table 27.10** Doses of therapeutic regimens

<b>Dose of the most common therapeutic regimens</b>	
<b>Nivolumab + ipilimumab<sup>a</sup></b>	Ipilimumab, 1 mg/kg IV plus nivolumab, 3 mg/kg IV, every 3 weeks for 4 doses followed by nivolumab, 3 mg/kg IV, every 2 weeks continuously until progression or intolerance.
<b>Pazopanib<sup>b</sup></b>	800 mg oral daily (on an empty stomach)
<b>Sunitinib<sup>c</sup></b>	50 mg oral daily, for 4 weeks, every 6 weeks (schema 4/2), or for 2 weeks, every 3 weeks (schema 2/1)
<b>Cabozantinib<sup>d,e</sup></b>	60 mg oral daily
<b>Axitinib<sup>f</sup></b>	5 mg oral, twice daily, with dose increase, if good tolerance, up to 10 mg oral twice daily
<b>Lenvatinib + everolimus<sup>g</sup></b>	Lenvatinib, 18 mg oral daily plus everolimus, 5 mg oral daily
<b>Nivolumab<sup>h</sup></b>	3 mg/kg IV, every 2 weeks
<b>Everolimus<sup>i</sup></b>	10 mg oral daily

<sup>a</sup>Motzer RJ, Tannir NM, McDermott DF et al (2018) Nivolumab plus Ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 378:1277

<sup>b</sup>Motzer RJ, Hutson TE, McCann L et al (2014) Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med* 370:1769

<sup>c</sup>Motzer RJ, Hutson TE, Tomczak P et al (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 27:3584

<sup>d</sup>Choueiri TK, Halabi S, Sanford BL et al (2017) Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol* 35:591

<sup>e</sup>Escudier B, Eisen T, Stadler WM et al (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 356:125–134

<sup>f</sup>Rini BI, Escudier B, Tomczak P et al (2011) Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 378:1931

<sup>g</sup>Motzer RJ, Hutson TE, Glen H et al (2015) Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol* 16:1473

<sup>h</sup>Escudier B, Motzer RJ, Sharma P et al (2017) Treatment beyond progression in patients with advanced renal cell carcinoma treated with Nivolumab in CheckMate 025. *Eur Urol* 72:368

<sup>i</sup>Motzer RJ, Barrios CH, Kim TM et al (2013) Record-3: phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 31(suppl):abstr 4504

## 27.8 Future Developments

The treatment setting for RCC is shifting to the incorporation of VEGF-targeted therapies in combination with immunotherapy. This synergy was confirmed by phase III study IMmotion151, which demonstrated benefit in PFS to atezolizumab + bevacizumab versus sunitinib (11.2 versus 8.4 months; HR 0.83,  $p = 0.0219$ ), and with even greater benefit in PDL1 positive individuals (HR 0.74, 95% CI 0.57–0.96,  $p = 0.0217$ ) [99, 100]. A Phase Ia/Ib study with 52 untreated metastatic kidney cancer patients tested the combination of pembrolizumab plus

**Table 27.11** Drugs approved for first- and second-line treatment of mRCC<sup>a</sup>

Approval first-line treatment						
Drugs	Arms	Setting	ORR	PFS	OS	Dosage
<b>Nivolumab + Ipilimumab (mAB)<sup>a</sup></b>	Nivolumab + Ipilimumab vs sunitinib	Intermediate Or Poor prognosis	42% vs 27%	11.6 m vs 8.4 m, HR 0.82	NR; HR: 0.63	IPI 1 mg/kg iv every 3 weeks + NIVO 3 mg/kg every 3 weeks for 4 doses followed by NIVO 3 mg/kg every 2 weeks
<b>Cabozantinib (TKI)<sup>c</sup></b>	Cabozantinib vs sunitinib	Intermediate Or Poor prognosis	46% vs 28%	8.2 vs 5.6 m, HR: 0.66	NSS	CABOZANTINIB 60 mg oral daily
<b>Bevacizumab (mAB)<sup>d</sup></b>	IFN + BV vs IFN + placebo IFN + BV vs IFN	Good or Intermediate prognosis	31% vs 13% 25.5% vs 13%	10.2 m vs 5.4 m, HR 0.68 8.5 m vs 5.2 m, HR 0.71	NSS	BV 10 mg/kg iv every 2 weeks + IFN 9 MU 3 times per week for 1 year
<b>Sunitinib (TKI)<sup>e</sup></b>	SUNITINIB vs IFN	Good or Intermediate prognosis	39% vs 8%	11 m vs 5 m, HR 0.54	NSS	SUNITINIB 50 mg oral daily, 4:2
<b>Pazopanib (TKI)<sup>f,g</sup></b>	PAZOPANIB vs placebo	Good or Intermediate prognosis	30% vs 3%	9.2 m vs 4.2 m, HR 0.46	NSS	PAZOPANIB 800 mg oral daily
<b>Temsirolimus (mTOR inhibitor)<sup>h</sup></b>	TEMSIROLIMUS vs IFN vs IFN + TEMSIROLIMUS	Poor prognosis, non-clear cell RCC included	8.6% vs 4.8% vs 8.1%	5.5 m vs 3.1 m vs 4.7 m	10.9 m vs 7.3 m vs 8.4 m	TEMSIROLIMUS 25 mg iv weekly
Approval second-line treatment						
<b>Nivolumab (mAB)<sup>i</sup></b>	NIVOLUMAB vs EVEROLIMUS	After progression to TKI therapy	25% vs 5%	4.6 vs 4.4 m HR 0.88	25 m vs 19 m, HR 0.73	NIVOLUMAB 3 mg/kg i.v. every 2 weeks
<b>Axitinib (TKI)<sup>j</sup></b>	AXITINIB vs SORAFENIB	After progression to TKI therapy	19.4% vs 9.4%	6.7 m vs 4.7 m, HR 0.67	NSS	AXITINIB 10 mg oral twice daily
<b>Cabozantinib (TKI)<sup>k</sup></b>	CABOZANTINIB vs EVEROLIMUS	After antiangiogenic therapy	57% vs 11%	7.4 vs 3.9 m, HR 0.51	21.4 vs 16.5 m, HR 0.66	CABOZANTINIB 60 mg oral daily
<b>Lenvatinib (TKI)<sup>l</sup></b>	LENVATINIB with EVEROLIMUS, EVEROLIMUS, LENVATINIB alone	After antiangiogenic therapy	43% vs 6% vs 27%	14.6 vs 5.5 vs 7.4 HR 0.4	NSS	LENVATINIB: 18 mg oral daily with EVEROLIMUS 5 mg oral daily
<b>Sorafenib (TKI)<sup>m</sup></b>	SORAFENIB vs placebo	Citokine refractory mRCC	10% vs 2%	5.5 m vs 2.8 m, HR 0.44	NSS	SORAFENIB 400 mg oral twice daily

<sup>a</sup>Sánchez-Gastaldo A et al (2017) Systemic treatment of renal cell cancer: a comprehensive review. *Cancer Treat Rev* 60:77–89

<sup>b</sup>Motzer RJ, Tannir NM, McDermott DF et al (2018) Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 378:1277

<sup>c</sup>Choueiri TK, Halabi S, Sanford BL et al (2017) Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol* 35:591

<sup>d</sup>Bracarda S, Bellmunt J, Melichar B et al (2011) Overall survival in patients with metastatic renal cell carcinoma initially treated with bevacizumab plus interferon-α2a and subsequent therapy with tyrosine kinase inhibitors: a retrospective analysis of the phase III AVOREN trial. *BJU Int* 107:214

<sup>e</sup>Motzer RJ, Hutson TE, Tomczak P et al (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 27:3584

(continued)

**Table 27.11** (continued)

<sup>1</sup>Motzer RJ, Hutson TE, McCann L et al (2014) Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med* 370:1769

<sup>2</sup>Escudier B, Porta C, Bono P et al (2014) Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study. *J Clin Oncol* 32:1412

<sup>3</sup>Hudes G, Carducci M, Tomczak P et al (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 356:2271

<sup>4</sup>Escudier B, Motzer RJ, Sharma P et al (2017) Treatment beyond progression in patients with advanced renal cell carcinoma treated with Nivolumab in CheckMate 025. *Eur Urol* 72:368

<sup>5</sup>Rini BI, Escudier B, Tomczak P et al (2011) Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 378:1931

<sup>6</sup>Choueiri TK, Escudier B, Powles T et al (2015) Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 373:1814

<sup>7</sup>Motzer RJ, Hutson TE, Glen H et al (2015) Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol* 16:1473

<sup>8</sup>Hutson TE et al (2014) Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 32(8):760–767

NSS no statistical significance

axitinib. This trial demonstrated a overall response rate of 73%, however the rate of grade 3 and 4 toxicity was 65% (hypertension, diarrhea and fatigue) [101, 102, 103]. There is an ongoing phase III trial that may will confirm these results (NCT02853331) 3. Other phase III studies are currently underway, studying Avelumab plus axitinib versus sunitinib (NCT02684006) [104, 105], Lenvatinib plus everolimus versus lenvatinib plus pembrolizumab versus sunitinib (NCT02811861) [106, 107] and Nivolumab plus carbozantinib versus nivolumab plus ipilimumab plus carbozantinib versus sunitinib (NCT03141177) [99].

New approaches to salvage tumor immunological recognition through autologous cellular immunotherapy are under development in patients with renal cell carcinoma (RCC). Patients undergoing cytoreductive nephrectomy were treated with sunitinib and serial intradermal injections of AGS-003 (rocapuldence-T), an immunotherapy with autologous dendritic cells processed with amplified tumor RNA plus synthetic CD40L RNA. Treatment was continued until disease progression. The median PFS was 11 months (95% CI 6.0–19.4) and the median overall survival was 30 months (95% CI 9.4–57.1) [101] Based on these results, the phase III study ADAPT (NCT01582672) [104] is being conducted.

In the adjuvant setting, immunotherapy has been studied. Pembrolizumab (NCT03142334) [106], atezolizumab (NCT03024996) [108] and the combination of Nivolumab plus ipilimumab (NCT03138512) [109] were included in the studies.

Although clinical trials may take many years to complete, we hope to update them with hopefully positive results and improvements in the survival of patients with these drugs.

### Key Points

- Kidney cancer is not a single disease, and the classification of renal tumors is based on morphology, histology, and genetic abnormalities
- The role of surgery in the management of kidney cancer includes the use of nephron-sparing approaches, cytoreductive nephrectomy, and metastasectomy
- Clinical prognostic models like IMDC in renal cell carcinoma are important tools for decision making and risk strategy in clinical trials
- The understanding of molecular biology and immunology in kidney cancer has translated into the development of new drugs, modified the natural history of the disease and streamlined the treatment algorithm.

## 27.9 Questions

1. Men, 40 years old, obese, dyslipidemic, hypertensive, reporting mild abdominal pain, diarrhea, nausea and fever. Exams include a computed tomography (CT) scan of the abdomen showing a 1.5 cm renal mass in the upper left pole suggestive of renal cell carcinoma. Systemic staging revealed no metastases. The patient underwent partial laparoscopic nephrectomy and the anatomicopathological examination revealed a renal granule cell carcinoma of 2.5 cm. The most appropriate next step is:

- A. Lymphnode dissection
- B. Adjuvant pazopanib
- C. Adjuvant radiotherapy
- D. Pathology report review
- E. Adjuvant Ipilimumab plus nivolumab

**CORRECT = (D)** Renal cell cancer is divided into clear cells and not clear cells (papillary, chromophobe and collecting duct tumors). The term granular cell carcinoma is currently not an acceptable pathological classification, and the surgical specimen should be subjected to a second analysis.

2. Man, 78 years, underwent partial nephrectomy for clear cell carcinoma of the kidney. After 10 years he presented with pathological fracture in the left hip, Performance status KPS 100% and analysis showed normal calcium, hemoglobin and LDH; The most appropriate course of action is:

- A. Radiation therapy
- B. High dose of interleukin-2
- C. Orthopedic tumor resection with reconstruction followed by radiation.
- D. Temsirolimus
- E. Nivolumab

**CORRECT = (C)** Patients with oligo metastatic disease and a long interval between the initial diagnosis and recurrent metastatic disease usually have a good prognosis. Thus aggressive resection, including orthopedic stabilization,

is indicated. High dose of IL-2 is approved for metastatic renal cancer, but because of its toxicity it would not be advisable for a 78-year-old woman just as Temezirolimus is indicated only for tumors at Motzer high risk criteria.

3. Which of the following criteria are apparently not associated with the development of clear cell renal carcinoma:

- A. Obesity
- B. Abusive use of analgesics
- C. Hypertension
- D. Tobacco abuse
- E. Familial adenomatous polyposis

R = (E) Apparently familial adenomatous polyposis are not associated with clear cell carcinoma.

4. The histological subtype of renal carcinoma, which is related to sickle cell anemia, is carcinoma.

- A. Clear Cell
- B. Sarcomatoid
- C. Of the collecting ducts
- D. Chromophobic
- E. Papillary

CORRECT = (C) Medullary carcinoma is the type of collecting duct carcinoma and occurs more frequently in patients with sickle cell disease.

5. A 52-year-old female with internal dyspnea. Diagnosis of renal mass at approximately 10 cm and tomography of the thorax reveals multiple secondary nodules in the lung. Laboratory tests reveal 11 mg of calcium and 2.2 of creatinine. Low-risk characteristics include, but are not limited to:

- A. Anemia
- B. Hypercalcemia
- C. KPS 50%
- D. Age over 60 years
- E. Chronic renal failure

CORRECT = (D) Hypercalcemia, poor performance status and anemia are important prognostic factors in most studies. Age, in and of itself, is not a prognostic factor.

6. In relation to the PREVIOUS QUESTION, the least indicated therapy in this case is:

- A. Temezirolimus
- B. Interferon + bevacizumab
- C. Pazopanib
- D. Sorafenib
- E. Sunitinib

R = (A) Temezirolimus is indicated only to patients with poor prognosis.

7. A 30-year-old man, white, presents bilateral complex cysts suspected of malignancy. Father with history of pheochromocytoma and uncle with pancreatic islet tumor. The most likely family syndrome is:

- A. Birt-Hogge-Dube Syndrome
- B. von Hippel-Lindau syndrome
- C. Hereditary renal cancer
- D. Fanconi's syndrome
- E. Hereditary leiomyomatosis and renal cancer

**CORRECT = (A)** von Hippel-Lindau disease, caused by mutations of the VHL gene, is an autosomal dominant cancer syndrome characterized by multiple renal cysts, early onset and multiple tumors, retinal angiomas and central nervous system hemangioblastoma, pheochromocytoma and pancreatic islet cell tumors.

8. Which of the following statements about the VHL gene is incorrect?

- A. is located on chromosome 3p25
- B. In situations of hypoxia or defective function of the VHL gene and protein, HIF is not destroyed and accumulates, leading to the transcription of hypoxia-inducible genes
- C. is part of a ubiquitin ligase complex
- D. The expression is regulated by vascular endothelial growth factor
- E. The mTOR family is part of

**CORRECT = (D)** VHL is part of the normal system of oxygen detection and the system of response of all cells, expressed constitutionally, and is mutated or modified in more than 60% of sporadic clear cell carcinomas of the kidney.

9. A 60-year-old woman with a previous medical history of uterine leiomyomatosis is diagnosed with renal mass with multiple lung nodules. Her mother and her sister had died of metastatic kidney cancer at age 55 and 40, respectively. Which of the following histological subtypes of renal cancer is most likely?

- A. Chromophobe
- B. Papillary type I
- C. Papillary type II
- D. Medullar
- E. Oncocytoma

**CORRECT = (C)** The hereditary leiomyomatosis syndrome is associated with mutations of loss of function in the Krebs cycle of the enzyme fumarate hydratase, leading to risk for cutaneous and uterine leiomyomas and type II solitary papillary renal carcinomas with aggressive clinical course.

10. Which medication choice represents LESS ADVERSE EFFECTS AND BETTER QUALITY OF LIFE?

- A. Pazopanib
- B. Sunitinib



- C. Everolimus
- D. Axitinib
- E. Doxorubicin

**CORRECT = (A)** Randomized phase III non-inferiority trial compared the efficacy and safety of pazopanib and sunitinib as first-line therapy. Although PFS for patients treated with pazopanib was not inferior to patients treated with sunitinib (HR, 1.05, 95% CI, 0.90, 1.22) and OS was similar (HR, 0.91, 95% CI, 0.76, 1.08), the safety profile favored pazopanib with less fatigue (63% vs. 55%), hand-foot syndrome (50% vs. 29%) and thrombocytopenia (78% vs. 41%). Health-related quality of life measures favor the use of pazopanib because it presents less fatigue, mucositis and hand-foot syndrome.

11. A 62-year-old male with metastatic clear cell carcinoma with diffuse bony involvement was treated with pazopanib in the last 8 months. Repeated imaging tests that show progression of liver disease. What treatment represents the next most appropriate step in management?
- A. Everolimus
  - B. Nivolumab
  - C. High dose of interleukin-2
  - D. Temsirolimus
  - E. Gementitabine

**CORRECT = (B)** Based on the phase III study, CheckMate-025, nivolumab demonstrated the benefit of nivolumab on everolimus in median overall survival (HR = 0.73; p = 0.018) in patients with advanced RCC who failed antiangiogenic therapy.

12. Patient seeking emergency for acute abdominal pain and computed tomography (CT) of the abdomen revealed gallstones and a complex mass of 3 cm in the left kidney. Normal renal function and other tests as well. What is the next step in the conduct?
- A. Return in 3 months with a new computed tomography
  - B. Resection of left renal mass
  - C. CT-guided fine needle aspiration (FNAB) of renal mass
  - D. Cholecystectomy
  - E. Abdominal ultrasound to characterize gallstones and renal mass

**CORRECT = (B)** Although a CT guided FNA of the renal mass can confirm the diagnosis, surgical intervention is still mandatory because FNA negative does not exclude malignancy.

13. A 51-year-old man, after a chronic abdominal pain, was submitted to investigation with CT scan, that revealed a 7-cm complex mass in the right kidney and multiples lung nodules measuring 1 to 2 cm. Fine-needle aspirates of the kidney mass and one of the lung nodules both revealed renal cell carcinoma. She has no comorbidities and has normal cardiac, pulmonary, and renal function. What is the recommendation in this case?

- A. The patient should undergo nephrectomy
- B. There is no reason for nephrectomy because the patient has metastatic disease
- C. Initiate pazopanib therapy and consider nephrectomy at a later time
- D. Nephrectomy would worsen this patient's quality of life
- E. Initiate sunitinib therapy and consider nephrectomy at a later time

CORRECT = (A) Nephrectomy can help manage symptoms caused by the primary tumor.

14. An 80-year-old woman diagnosed with renal clear cell carcinoma underwent radical nephrectomy 3 years ago. Currently with tumor recurrence in the liver, lymph nodes and lung. She is fully active and asymptomatic. Previous medical history includes a myocardial infarction followed by five-vessel myocardial revascularization surgery 5 years ago. Its cardiac ejection fraction has been between 40% and 50% for years. Complete blood counts are normal and serum creatinine is 2.5 mg/dL and stable since nephrectomy. How should this patient be managed.
- A. Metastasectomy
  - B. High-dose interleukin 2
  - C. Pazopanib or sunitinib
  - D. Everolimus
  - E. Subcutaneous interferon alfa

R = (C) Patient with metastatic disease and poor performance, the best treatment for these options would be pazopanib or sunitinib, effective first-line metastatic drugs for kidney cancer. Interleukin 2 would be a toxic treatment for this patient. Everolimus and interferon alpha are not approved in this scenario.

15. When we should not use Temezirolimus, except:
- A. Second metastatic line
  - B. Adjuvant Treatment
  - C. First high risk line
  - D. In combination with sunitinib
  - E. Neoadjuvant Treatment

CORRECT = (E) Temezirolimus is approved for first line treatment high risk patients.

## 27.10 Clinical Case

Woman, 50 years old, asymptomatic. In January of 2015, a CT scan showed a solid lesion with a necrotic component in the lower pole of the right kidney. She underwent left nephrectomy and segmental resection of the duodenum, with pathological diagnosis of renal cell carcinoma with sarcomatoid component representing 80% of

neoplasia (pT4pN0M0). Two years after, she presented with multiple pulmonary nodules bilaterally, the largest in LIE (27 mm). KPS 70%. She initiated systemic treatment with gemcitabine 1000 mg/m<sup>2</sup> (D1 and D8) and sunitinib 50 mg (D1 to D14) every 21 days. Needed delays and dose reductions due to grade 2 and 3 gastrointestinal and medullary toxicities. The best response was stable disease. In march 2017, after 7 cycles, had disease progression in the liver. In May 2017, it started nivolumabe 3 mg/kg every 15 days. He improved from KPS to 90%. In the first response evaluation, after the fourth cycle, it presented partial response. Patient follows treatment with sustained radiological response, clinical benefit and excellent tolerance.

### Questions

1. In patients with renal cell carcinoma with sarcomatoid component, what leads to choose combination of chemotherapy plus inhibitor of tyrosinokinase?

R = The presence of sarcomatoid component greater or less than 20%. For tumors with sarcomatoid component  $\geq 20\%$ , the best choice would be the association of sunitinib with gemcitabine. For tumors with components  $< 20\%$  in total tumor volume, the isolated anti-VEGF strategy seems sufficient (sunitinib, sorafenib or bevacizumab).

2. What is the role of the second line with immunotherapy or mTOR blocker in sarcomatoid component of renal cell carcinoma?

R = The sarcomatoid component occurs in 3–29% and gives greater aggressiveness, with mOS between 6 to 10 months if metastatic. It has resistance to chemotherapy and unsatisfactory responses to IL-2 immunotherapy. The pivotal study of anti-PD1 therapy (nivolumabe) in RCC post-anti-VEGF therapy excluded it. The PD1/PDL1 antigens represent a promising alternative, given the rationale that up to half of these tumors express PDL1, although this is still not a predictive factor of response.

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# Chapter 28

## Predictors of Oncologic Outcomes After Treatment of Urothelial Cancer



Kyle Spradling and Ramy F. Youssef

**Abstract** Despite modern advances in surgical procedures, morbidity and mortality rates remain unsatisfactory for patients treated for bladder cancer (BC) or upper tract urothelial cancer (UTUC). Conventional prognostic tools such as tumor grade, stage, and lymph node involvement are important predictors of oncologic outcomes, but additional prognostic factors have been established in recent years and may lead to improved treatment decision-making and oncologic outcomes for patients with BC or UTUC. The integration of several clinico-pathological and molecular biomarkers into multivariable prognostic models or nomograms has been shown to provide more accurate prognoses than grade and stage alone in patients with UC. In this chapter, we review the current prognostic factors for BC and UTUC, giving particular attention to clinico-pathological factors shown to be independent predictors of oncologic outcomes.

**Keywords** Bladder cancer · Upper tract urothelial cancer · Oncologic outcomes · Prognosis

### Abbreviations

BC	bladder cancer
RC	radical cystectomy
TUR	transurethral resection
UTUC	upper tract urothelial cancer
LVI	lympho-vascular invasion
CIS	carcinoma in situ
LND	lymph node dissection
DFS	disease-free survival
CSS	cancer-specific survival

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BCG	bacillus Calmette-Guerin
LN	lymph node
TCC	transitional cell carcinoma
SCC	squamous cell carcinoma
IBCC	International Bladder Cancer Consortium
BCRC	Bladder Cancer Research Consortium
RNU	radical nephroureterectomy
BMI	Body mass index

## 28.1 Prognostic Factors After Treatment of Bladder Cancer

### 28.1.1 Introduction

Bladder cancer (BC) is a common cause of morbidity and mortality in the United States with approximately 74,690 new cases diagnosed in 2014 [1]. While the majority of non-muscle-invasive BC is typically managed by transurethral resection (TUR) followed by intravesical therapy, the standard treatment for patients with muscle-invasive BC is radical cystectomy (RC) with or without neoadjuvant chemotherapy. Despite the continuing advances in surgical procedures, morbidity and mortality rates remain unsatisfactory after RC for patients with muscle-invasive BC. Five-year disease free survival (DFS) and cancer-specific survival (CSS) ranges between 50–70% after RC in this patient population [2–4]. Unsatisfactory outcomes after RC may be due to clinical understaging of disease, the presence of micrometastasis, or underutilization of systemic therapies [5, 6].

Clinico-pathological findings, such as tumor-node-metastasis (TNM) stage and tumor grade have traditionally served as prognostic tools, providing estimates of oncologic and survival outcomes for patients with BC. Various nomograms and prognostic models have also been developed to incorporate several prognostic factors to provide individualized predictions of survival and disease recurrence for patients undergoing RC [7–9]. Furthermore, the use of biomolecular markers may have potential to further improve predictive models and help clinicians select patients who may be the best candidates for systemic therapies following RC [10, 11].

## 28.2 Non-muscle-Invasive Bladder Cancer

### 28.2.1 Clinico-pathological Prognostic Factors

Non-muscle-invasive bladder cancer may present as pTa, pT1, or carcinoma in situ (CIS) lesions with the majority of cases (70%) being pTa disease [12]. Disease recurrence (50–80% of pTa patients) and disease progression (10–30% of pT1 and CIS patients) are the biggest threats for patients with non-muscle-invasive BC [12].

The most important clinico-pathological predictors for recurrence are multiplicity, tumor size, and rates of prior recurrences [12, 13]. The most useful predictors for progression are tumor grade, stage, and the presence of CIS, but these parameters also have some predictive value for disease recurrence as well [12, 13]. Sylvester and colleagues developed the European Organization for Research and Treatment of Cancer (EORTC) scoring system using six factors to estimate probabilities of recurrence and progression and defined patient risk into categories of low, intermediate and high. The European Association of Urology has subsequently incorporated this scoring system into its guidelines and the EORTC system has been shown to be a useful tool for identifying high-risk patients with non-muscle-invasive BC [12, 14].

### ***28.2.2 Transurethral Resection Quality***

Another important prognostic factor for determining recurrence and progression in patients with non-muscle-invasive BC is the quality of TUR [15, 16]. In up to 30% of patients receiving a re-TUR for pT1 or high grade tumors, upstaging may occur [12, 16]. Also, patients with high grade non-muscle-invasive BC have been shown to respond better to bacillus Calmette-Guerin (BCG) therapy following re-TUR [17]. In patients who develop residual tumors following initial resection, recurrence-free survival was significantly higher after 5 years follow-up in patients who received re-TUR (63%) compared to those who underwent only one TUR (40%) [18]. A complete TUR at the initial treatment or after disease recurrence is associated with a lower prevalence of residual tumors and higher rates of recurrence-free survival.

### ***28.2.3 Perioperative Intravesical Therapy***

Randomized clinical trials have shown that perioperative intravesical therapy after TUR for patients with non-muscle invasive BC is associated with decreased rates of disease recurrence [19]. Reduction in recurrence may be as high as 39% compared to patients who undergo TUR alone, and it was estimated that the number needed to treat in order to prevent one recurrence was 8.5 patients. Side effects associated with intravesical chemotherapeutic agents such as epirubicin or mitomycin C are generally mild; however, it should be noted that such treatments are contraindicated in cases in which bladder perforation is suspected.

Intravesical therapy with BCG has been shown to be an effective treatment option associated with a 32% reduction in disease recurrence [20]. Furthermore, intravesical BCG treatments have been shown to be superior to intravesical chemotherapy in randomized trials [21, 22]. Ten-year progression-free rates and disease-free survival are improved in patients receiving BCG intravesical therapy

[23]. Despite the beneficial effects of BCG therapy in these patients, it may still be an underutilized resource for high-risk patients with non-muscle invasive BC [24].

### **28.2.4 Early Radical Cystectomy**

Early RC is the treatment of choice for patients with high-risk non-muscle-invasive BC who fail BCG therapy or for patients with high risk of cancer progression [12, 13, 25]. Adverse prognostic factors such as micropapillary histology, concomitant CIS, high grade, solid architecture, and lymphovascular invasion (LVI) are associated with high risk of progression [26–28]. For the vast majority of high-risk patients, treatment of TUR followed by adjuvant BCG may represent the most reasonable strategy with the option to perform RC early if progression is detected [12].

## **28.3 Muscle-Invasive Bladder Cancer**

### **28.3.1 Lymph Node Status and Extent of Lymph Node Dissection**

For patients undergoing RC for muscle-invasive BC, the most significant predictor of oncologic outcome is the extent of lymph node (LN) involvement [29]. Five-year survival rates are 20–35% for patients with tumor metastasis to LNs [2–4]. A more extensive list of LN-related prognostic factors reported to be predictors of outcomes includes the number of positive LNs, the extent of lymphadenectomy and number of nodes removed, and the LN density [29–35]. While no well-defined guidelines for lymph node dissection (LND) during RC exist, numerous studies have suggested that extended LND is associated with better oncologic outcomes and lower risks of micrometastatic disease following RC [29, 30, 34, 36]. Furthermore, performing extended LND may provide more accurate staging. We are waiting for results of an important randomized trial that will tell us the optimal level of LND during RC in order to provide therapeutic benefit while minimizing unnecessary risks.

### **28.3.2 Tumor Stage**

The second most important predictor of oncologic outcomes after RC is tumor stage [2–4]. The determination of tumor stage may take place prior to RC by evaluating TUR pathology or radiographic images; however downstaging may occur in nearly

one quarter of cases [6], and this can have significant implications on how patients are selected for neoadjuvant therapies. Multi-institutional studies have shown that primary pT stage has significant prognostic value in muscle-invasive BC. The 5-year DFS of patients with pT0 or pT1 stage is 80–90% but those numbers drop to 20–40% in patients with pT4 stage [2–4]. Higher stages are associated with high risk of recurrence and mortality and may benefit from adjuvant or neoadjuvant chemotherapy.

### ***28.3.3 Tumor Grade***

While tumor grade has significant prognostic value in non-muscle invasive BC, it has not been shown to be a powerful predictor of oncologic outcomes in muscle-invasive bladder as nearly all patients undergoing RC will have high-grade disease [29]. Nevertheless, several grading systems have been developed to provide simple and reproducible tools for clinical use [37, 38].

### ***28.3.4 Lymphovascular Invasion***

The presence of lymphovascular invasion (LVI) in RC specimens has been shown to correlate with aggressiveness of BC and shown to be a prognostic predictor of oncologic outcomes independent of lymph node involvement [39–42]. In addition to transitional cell carcinoma (TCC), LVI is a prognostic factor after RC in patients with squamous cell carcinoma (SCC) of the bladder [43]. The presence of LVI may be a valuable prognostic tool when selecting patients undergoing RC for adjuvant or neoadjuvant chemotherapy.

### ***28.3.5 Nomogram as Outcome Prediction Models***

The integration of several prognostic factors into nomograms has been shown to provide more accurate prognoses than grade and stage alone in patients with BC [7, 8]. The International Bladder Cancer Consortium (IBCC) Nomogram incorporates prognostic factors such as age, grade, stage, LN status, and histological cancer type into the nomogram in order to calculate the risk of disease recurrence after RC. It has been shown to have a predictive accuracy of 75%. The Bladder Cancer Research Consortium (BCRC) Nomogram was similarly developed to predict oncologic outcomes after RC and incorporates grade, stage, LVI, presence of CIS, as well as use of adjuvant or neoadjuvant treatments [8]. Both of these nomograms have been externally validated and shown to be useful tools for patient counseling and selection for adjuvant therapies [44].

### **28.3.6 *Molecular Biomarkers for Predicting Oncologic Outcomes***

The integration of molecular biomarkers with existing nomograms improves the prognostic value and predictive accuracy of those nomograms [45–47]. Increased expression of several molecular biomarkers involved in cell cycle regulation, apoptosis and angiogenesis have been extensively studied and shown to be associated with advanced stage, grade, LVI, LN metastasis, DFS, and CSS in patients with BC [29] [48, 49] [50–52]. Furthermore, the assessment of multiple biomarkers or panels of biomarkers have been shown to be more accurate than assessments of individual biomarkers [45–47]. Evaluation of these biomarkers in patients being treated by RC has been shown to have significant prognostic value in terms of disease recurrence and progression and may be a useful predictor of upstaging in patients undergoing RC [53–55]. Importantly, panels of biomarkers may prove to be the most useful tool in identifying the most appropriate candidates for adjuvant or neoadjuvant chemotherapy.

## **28.4 *Prognostic Factors after Treatment of Upper Tract Urothelial Cancer***

### **28.4.1 *Introduction***

Upper tract urothelial cancers (UTUC) are rare compared to bladder tumors, accounting for only 5% of urothelial cancers [1]. Small, low grade UTUC can be treated endoscopically. However, the gold standard treatment for UTUC in patients with a healthy contralateral kidney remains radical nephroureterectomy (RNU) [56, 57]. Unfortunately, oncologic outcomes in patients with invasive UTUC remain unsatisfactory despite continuing advancements in surgical techniques and adjuvant chemotherapies [58]. Due to the rarity of UTUC, studying prognostic factors and predictors of outcomes remains challenging; however, large multi-center collaborations focusing on outcomes of UTUC after RNU have provided insight into several clinico-pathological prognostic factors [57]. These predictors of oncologic outcomes may help in clinical decision making and tailoring of treatments for patients with UTUC.

Prognostic factors such as lymphovascular invasion (LVI), sessile tumor architecture, concomitant carcinoma in situ (CIS), and a history of bladder CIS have been identified for patients with UTUC, but there still exists controversy regarding the prognostic value of factors like tumor location and tumor necrosis. While there does not exist a well-defined template for lymph node dissection (LND) for UTUC, LND may have significant prognostic value, provide better disease staging, and help identify candidates for adjuvant systemic therapy.

## **28.5 Clinical Prognostic Factors**

### **28.5.1 Age and Gender**

Age and gender do not appear to have a significant impact on outcomes of UTUC after RNU. While older patients have been shown to have lower DFS and CSS after RNU, these differences are unlikely to be due to differences in the biological behavior of UTUC [59]. In fact, it has been shown that elderly patients may be successfully cured of UTUC with RNU, so aggressive surgical treatment should be considered in this patient population [60]. Similarly, gender does not seem to affect the behavior of UTUC or oncologic outcomes after RNU [61].

### **28.5.2 Obesity**

Obesity appears to be an independent predictor of patient outcomes in patients undergoing RNU for UTUC. Body mass index (BMI) greater than 30 was shown to adversely affect both 5-year DFS and CSS rates compared to patients with normal BMI (<25) [62].

### **28.5.3 Hydronephrosis**

Evaluation for hydronephrosis has been shown to be a valuable step in assessing the extent of disease in patients with UTUC. The presence of hydronephrosis is associated with advanced disease and overall poorer oncologic outcomes for patients undergoing RNU [63, 64]. Using hydronephrosis as a prognostic factor, patients can be identified as having higher risk of non-organ confined disease and selected for neoadjuvant or adjuvant chemotherapies.

## **28.6 Pathological Prognostic Factors**

### **28.6.1 Tumor Stage**

The most important predictor of oncologic outcomes in patients with UTUC remains the tumor stage. Increasing pathological stage is associated with greater potential for metastatic disease and lower DFS and CSS [57]. In fact, for patients with stage T4 UTUC, the five-year DFS drops to less than 5%. Chemotherapy combined with aggressive RNU may represent the best treatment option for patients with high stage disease in order to provide some improvement in prognosis [65].

### **28.6.2 Tumor Grade**

Tumor grade is also an important prognostic factor and predictor of DFS and CSS in patients with UTUC, and has been shown to be one of the most useful parameters in treatment decision-making [57]. The majority of patients with UTUC will have high-grade tumors at the time of RNU; however, grade was the most important prognostic factor in preoperative nomogram for detection of non-organ confined UTUC [66]. The nomogram can be used for patient counseling, guiding the extent of LND during RNU, or selection of neoadjuvant chemotherapy for patients.

### **28.6.3 Lymph Node Status and Extent of Lymph Node Dissection**

Lymph node status is an important prognostic factor in UTUC and has been shown to predict DFS and CSS [57] [67, 68]. Patients with positive LN status have significantly worse outcomes after RNU compared to patients with negative LNs. Approximately 20–25% of patients with UTUC may have positive LNs at the time of RNU [57, 68]. In addition, higher stage tumors were found to have higher probability of LN metastasis [68]. Therefore, LND in patients with higher stage tumors may help with treatment decision-making and selection for adjuvant chemotherapy. The extent of LND may be associated with better oncologic outcomes. According to Roscigno and colleagues, a minimum of eight removed LNs may be needed during LND to provide adequate information regarding LN status [69, 70]. Despite these findings, LND is only performed in about half of RNU cases for UTUC in academic institutions [67]. Prospective clinical trials are needed to help create standardized guidelines and templates for LND during RNU for UTUC.

### **28.6.4 Lymphovascular Invasion**

Lymphovascular invasion (LVI) has been shown to be an important predictor of oncologic outcomes in UTUC, and it is an independent predictor of DFS and CSS [57, 71, 72]. LVI is found in approximately 25% of RNU specimens in patients with high stage or high grade UTUC. Incorporating LVI into a predictive model with conventional pathological findings, such as tumor stage and grade, significantly improves the accuracy of outcome prediction [71]. Therefore, it is important to consider LVI status when assessing risk for recurrence or tumor progression.



### **28.6.5 Tumor Architecture**

A number of other pathological factors have been shown to have significant prognostic value in UTUC. Sessile tumor architecture has been shown to be an independent predictor of oncologic outcomes after RNU and associated with tumor aggressiveness when compared to papillary architecture [57, 73, 74].

### **28.6.6 Carcinoma In Situ**

The presence of concomitant CIS in patients with UTUC is associated with more aggressive tumor pathology and is an independent predictor of tumor recurrence after RNU [75, 76].

### **28.6.7 Tumor Necrosis**

The presence of significant tumor necrosis in RNU specimens was shown to be an independent predictor of oncologic outcomes. Greater than 10% necrosis was associated with features of tumor aggressiveness, including LN metastasis, LVI, and high stage and pathologic grade [77, 78].

### **28.6.8 Tumor Location**

Tumor location may have a significant impact on oncological outcomes in patients undergoing RNU. Some evidence suggests that tumors located at the ureteroenteric junction may be associated with more aggressive features and poor outcomes; however, these findings are still debatable [79]. Additional studies are needed to validate these findings before tumor necrosis and tumor location can be used as prognostic factors to guide treatment decisions after RNU.

### **28.6.9 Nomograms for UTUC**

The combination of several prognostic factors may help improve prediction of oncologic outcomes after RNU in patients with UTUC. Recent multi-institutional collaboration studies have generated nomogram models to predict outcomes based on multiple clinico-pathological factors [66, 80–82]. These nomograms have been

shown to accurately predict DFS and CSS in patients with low or high-grade disease. Furthermore, nomograms may be seamlessly integrated into clinical practice as tools for patient counseling, scheduling patient follow-ups, and selecting patients for multimodal therapies.

### **28.6.10 Future Prognostic Markers of UTUC**

Despite the growing body of evidence supporting the use of adjuvant and neoadjuvant chemotherapies in the management of UTUC, few patients undergoing RNU receive perioperative therapies [83, 84]. The use of biomarkers beside clinico-pathological prognostic factors will play an increasingly important role in guiding clinical decision-making and the selection of candidates for adjuvant therapies. Similar to studies on molecular biomarkers of BC, several studies are ongoing to identify molecular biomarkers that have significant prognostic value for UTUC [85–87]. The development of improved predictive models incorporating biomarkers may improve the accuracy of current prognostic models and lead to individualized multimodal treatment strategies for patients and improved oncologic outcomes for patients with UTUC.

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# Chapter 29

## Germ-Cell Tumors



Giannis Mountzios

**Abstract** Cancer originating from germ cells is a special disease, characterized by increased incidence in young men (18–40 years) and extremely good prognosis, even if it is diagnosed in advanced stages. The vast majority of these cancers are originated in the gonads (testicles), while a small percentage of germ cell tumors may appear in midline extragonadal locations that are embryologically developed from the central crest (epiphysis, mediastinum, retro peritoneum).

**Keywords** Germ cell tumors · Testicular cancer · Seminoma · Non-seminoma · Yolk sac · Teratoma · Embryonal carcinoma

Cancer originating from germ cells is a special disease, characterized by increased incidence in young men (18–40 years) and extremely good prognosis, even if it is diagnosed in advanced stages. The vast majority of these cancers are originated in the gonads (testicles), while a small percentage of germ cell tumors may appear in midline extragonadal locations that are embryologically developed from the central crest (epiphysis, mediastinum, retro peritoneum).

### 29.1 Testicular Cancer

#### 29.1.1 *Epidemiology – Genetic Background- Molecular Biology*

Although testicular cancer represents only 1% of solid tumors in adults, in a ratio of 3: 100,000 males per year, it is the most common malignancy among young adults aged between 16 and 40 years. The last 40 years, the incidence of testicular cancer has doubled worldwide and currently the likelihood of a caucasian male developing testicular cancer during his lifetime is 0.2%. The incidence of the disease is 5: 1 in Caucasians compared to other race populations and it is more common in the

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developed countries of North America and North-Western Europe, who follow the Western lifestyle and dietary habits.

An important risk factor for developing testicular cancer is cryptorchidism, with the relative risk ranging from 8.8 to 40. In addition to that, any disease associated with dysgenetic gonads, such as in Down and Klinefelter syndromes, as well as acquired inflammations in testicular parenchyma, such as viral orchitis caused by Mumps or HIV viruses, are associated with increased incidence of testicular cancer. However, despite the influence of environmental (epigenetic) factors, epidemiological and linkage studies provide evidence for a genetic basis of the disease, at least in a number of families. For the brothers of a male testicular cancer patient it is 10 times more likely to develop testicular cancer compared to the general population while their male progenies bear a 4 times higher risk, usually with an early onset of the disease.

Cytogenetic studies showed that, almost in every case, germ cell tumors of the testis are hyperdiploid. The most commonly associated genetic disorder is the presence of an extra copy of the short arm of chromosome 12 (isochromosome 12p) and a loss of the long arm of the same chromosome. Latest data implicate the cyclin D2 gene, which is an important modulator of the G1/S cell cycle checkpoint, as the carrier of the genetic disorder. Based on this theory, more recent preclinical studies showed that an abnormal chromatid might be responsible of exchanging and recombining DNA segments during meiosis and eventually leading in creating extra copies of 12p in the germ cell, the overexpression of cyclin D2 and finally the continuous activity of the cell cycle and the accumulation of genetic lesions. The original invasive germ cell tumors are characterized by molecular abnormalities in the retinoblastoma gene (RB1) pathway, including the upregulation of cyclin D2 and p27 and the deregulation of RB1 and the Cyclin-dependent kinases inhibitors p16, p18, p19 and p21. These synergistic effects, associated with abnormalities in the receptor of the growth factor gene, are valued as pathognomonic abnormalities of embryonic cell tumors, which are rarely found in other types of tumors.

### **29.1.2 Histology**

Classified by their histology, the germ (stem) cell tumors of the testicles are broadly divided in two types: the seminoma (seminomatous germ cell tumors) and non seminomatous germ cell tumors. Both types are developed from the mature or maturing testis seminal epithelium. Non seminomatous tumors differentiate into one or more embryonic structures with similar morphological and histological characteristics, and therefore the majority of these tumors appear to have mixed morphology (mixed non seminomatous tumors). In this case, four basic types on non seminomatous tumors can be identified: (a) embryonal carcinoma, (b) mature and immature teratoma, (c) choriocarcinoma and (d) yolk sac tumor. It has to be noted that in the same tumor two or more different patterns or even metastasis with histological features of a more differentiated (later in the developmental process) histology might appear,

eg. choriocarcinoma in relapsed yolk sac tumor, resulting to several combinations (mixed seminomatous along with non seminomatous tumors or mixed non seminomatous tumors).

The set of the most frequent histological subtypes of testicular tumors is mentioned in the following table:

#### **I. Stem cell tumors**

- A. Intratubular germ cell neoplasia (in situ)
- B. Seminoma
- C. Spermatocytic seminoma
- D. Embryonic carcinoma
- E. Yolk sac tumor
- F. Choriocarcinoma
- G. Teratoma
- H. Monodermal varieties
- I. Mixed tumors

#### **II. Germ line cell tumors**

- A. Interstitial or Leydig cell tumor
- B. Sertoli cells tumor

#### **III. Mixed germ cell and germ line tumors**

- Gonadoblastoma

### **29.1.3 Clinical Evaluation-Diagnosis**

Testicular tumors are generally developed in young men during their third to fourth decade of life. In 78% of the cases, the disease appears in men aged 20–40 years, 20% in men >40 years, and 2% in boys under 18 years. Usually patients present with a painless, unilateral mass in the scrotum, found incidentally. In 20% of cases the first symptom is pain in the scrotum or feeling of heaviness in the area, while up to 30% of patients have local pain when palpating the testis. More rarely the disease is diagnosed by physical examination for accidental injury of the scrotum. Pain in loins occurs in a 10% of cases (due to retroperitoneal metastases). In a percentage of 10% the tumor mimics orcheoepididymitis often resulting in delayed diagnosis, while rarely gynecomastia may occur, mostly in choriocarcinoma cases. Often the tumor can be accompanied by hydrocele and this why, if in doubt, a scrotum ultrasound should be prescribed. In case of metastases, the first manifestation of the disease may be shortness of breath or cough (pulmonary metastasis), skeletal pain (bone metastases), headache, neurological signs or symptoms in the central nervous system (brain metastases). The differential diagnosis of testicular cancer involves ruling out epididymitis or orcheoepididymitis, hydrocele, spermatocele, haemocele, granulomatous orchitis, varicocele and epidermoid testis cyst or epididymis.

### **29.1.4 Staging**

After the diagnosis, the surgical resection (radical orchiectomy) and the histological characterization of the tumor, the complete staging of disease follows. A complete staging requires both imaging exams to ascertain if there are enlarged para-aortic, retroperitoneal and mediastinal lymph nodes or lesions of liver or lung, as well as the evaluation of tumor markers, beta- human chorionic gonadotropin and alpha – fetoprotein both preoperatively and postoperatively. Notably that beta – chorionic gonadotropin ( $\beta$ -hCG) increases in cases of non seminomatous tumors since rarely a seminoma contains syncytiotrophoblastic and cryptotrophoblast elements, while the alpha- fetoprotein increases only in case of non seminomatous tumors containing elements of embryonic-cell carcinoma or yolk sac tumor. The half-life for alpha – fetoprotein is 5–7 days and for beta – human chorionic gonadotropin is 2–3 days. Thus the detection of high levels after orchiectomy is indicative of residual disease. Brain CT and bone scans are performed only when clinically indicated. Based on these criteria, the disease is classified as stage I, II or III, as shown in Table 29.1. Stage I disease refers to cancer limited to the testis, stage II disease refers to the presence of enlarged subdiaphragmatic lymph nodes and stage III refers to disease that has spread to the diaphragm or parenchymal sites.

It is acknowledged that patients with stage II and III disease are a heterogeneous group with different prognosis and that the integration of tumor marker tests in this classification could provide better distinction between prognostic groups. One of the most important steps in this field was the international classification of the International Germ Cell Cancer Collaborative Group (IGCCCG). This group designated the relevant outcomes to each group of patients and has made the treatment approach more rational: Young patients who belong to low-risk group will take less aggressive therapy with emphasis on preventing toxicity from unnecessary treatments, while patients in high risk group should receive more toxic treatment, with a higher threshold of acceptance risks of late effects, in order to provide the best chances for long-term survival (Table 29.2).

### **29.1.5 Treatment**

#### **29.1.5.1 Orchiectomy**

The surgical resection of the affected testicle is usually performed before any other therapeutic manipulation. Especially patients with rampant metastatic disease, which is life threatening, receive adjuvant chemotherapy followed by orchiectomy. Radical orchiectomy is performed through an inguinal intersection. Followed by the en block removal of the testis, along with the tunica and the spermatic cord up to the medial inguinal orifice. Patients with preoperatively negative plasma tumor markers test, and small, (probably benign) tumors, a statistical analysis based on quick core biopsies should be preceded to avoid an unnecessary orchiectomy and allow a smaller coherence with organ preservation.

**Table 29.1** AJCC-UICC TNM testicular cancer classification

Testicle (T)	II
pTis	Intratubular, in situ
pT1	Testis and epididymis, without vascular/lymphatic invasion
pT2	Vascular/lymphatic invasion, extending through the tunica albuginea and tunica vaginalis
pT3	Invasion of spermatic cord
pT4	Scrotum invasion
<b>Retroperitoneal lymph nodes</b>	
N1	<2 cm
N2	2–5 cm
N3	>5 cm
<b>Metastases</b>	
M1a	Nonregional ( ) nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung
<b>Plasma biomarkers</b>	
S1	LDH < 1.5 N, HCG < 5000 IU/l AFP < 1000 ng/ml,
S2	LDH 1.5–10 N, HCG 5.000–50.000 IU/l AFP 1000–10.000 ng/ml
S3	LDH >10 N, HCG >50.000 IU/l AFP > 10.000 ng/ml
<b>Stage</b>	
0	pTisN0M0 Sx
I	pT1–4 N0 M0, S0-Sx
IIA	pTany, N1 M0, S0-S1
IIB	pTany, N2 M0, S0-S1
IIC	pTany, N3 M0, S0-S1
IIIA	pTany, Nany M1a, S0-S1
IIIB	pTany, Nany M0, S2
	pTany, Nany M1a, S2
IIIC	pTany, Nany M0, S3
	pTany, Nany M1a, S3
	pTany, Nany M1b, Sany

**29.1.5.2 Stage I Seminoma**

The recurrence rate after orchectomy rises to 15–20%, if not followed by adjuvant chemotherapy. Treatment options for stage I seminoma include surveillance, radiotherapy and chemotherapy.

The advantage of mere surveillance is the fact that 80% of the patients will not be subjected to a treatment that might be eventually unnecessary, given that they would not relapse and therefore they could be spared the consequent toxicity. However, even in case of relapse, the cure rate remains high. On the other hand, surveillance is not only an intensive and long procedure but it also requires a high

**Table 29.2** IGCCCG international classification

Non seminomas	Seminomas
<b>Good prognosis</b>	
Primary testicular tumor or retroperitoneal without non-pulmonary intestinal metastases and biomarkers S1 level (56%, 92% 5-year survival)	Any primary site without non-pulmonary intestinal metastases and any level of plasma biomarkers (90%, 86% 5-year survival)
<b>Intermediate prognosis</b>	
Primary testicular or retroperitoneal tumor without non-pulmonary intestinal metastases and biomarkers S2 level (26%, 5-year survival 80%)	Any primary site with non-pulmonary intestinal metastases and any level of plasma biomarkers (10%, 73% 5-year survival)
<b>Poor prognosis</b>	
Primary tumor in the mediastinum with pulmonary intestinal metastases or biomarker S3 level (16%, 48% 5-year survival)	None

level of compliance from the patient's side and entails feelings of stress and fear of relapse risk. In general, this method is suggested for stage I seminoma patients, with no evidence of risk factors (tumor size <4 cm and absence of rete infiltration).

The original treatment for stage I seminoma was radiation therapy, based on the known radiosensitivity of seminomatous cells. The treatment field only involved the paraaortic and iliac lymph nodes. Due to that recurrence occurred in as many as 10% of patients, the efforts were focused in field size and dose reduction. Currently, only paraaortic lymph nodes are included in the standard treatment field and the prescribed dose is 2000 rads.

Chemotherapy is the standard treatment in most of the European countries, for patients with stage I disease and increased risk of relapse (tumor size >4 cm, rete testis infiltration). Chemotherapy is increasing the cure rates to 98% for those. The currently used regime is either 2 cycles of carboplatin, dosed at AUC 6 or one cycle dosed at AUC 7.

### 29.1.5.3 Stage I Non-seminomas

Treatment choices include mere surveillance, adjuvant chemotherapy and retroperitoneal lymph node dissection. Mere surveillance, as in the case of seminomas, involves a fairly intensive surveillance protocol, which requires a great deal of patients' cooperation and it applies only when there is no evidence of risk factors. Those prognostic factors, as emerged from studying a number of stage I non seminoma patients, include tumor size, tunica vaginalis and sperm cord infiltration, the a-FP element in the histological subtype and the presence of neoplastic emboli in the testicular venous network. Recurrence, which rates between 15–20%, usually occurs within the first 2 years of surveillance and thus, the surveillance protocol is more thorough in the beginning, comprising monthly clinical examination, tumor biomarker evaluation every 2 months and imaging assessment every 3 months.

Preventive retroperitoneal lymph node dissection is a choice of treatment based on data showing that the majority (97%) of lymph node relapse in stage I non seminomas refers to pelvic, paraaortic and retroperitoneal lymph nodes and the cure rates are between 95–97%. On the other hand, this method requires a surgical handling, which is not only demanding in technical terms but also bears an increased likelihood of causing retrograde ejaculation, due to severing of the inner pudendal plexus (5–10%). Also, an 80% of patients are subjected to surgery, even though they are not going to relapse. For this reason, this technique is currently applied only in specialized centers, mostly in the USA and it is less popular in Europe.

The administration of adjuvant chemotherapy is the most common therapeutic choice for patients with stage I non seminomatous tumors that present one or more risk factors. Currently, the standard regimen is BEP (bleomycin, etoposide, cisplatin), which is administered in two five-day-cycles, every 3 weeks and increases cure rate up to 97%. The main toxic effects are marrow suppression, nausea-vomiting, alopecia, nephrotoxicity which requires intensive hydration before and after the administration of cisplatin and pulmonary toxicity associated with bleomycin, requiring pretreatment and posttreatment monitoring of respiratory function. Moreover, due to gonadal suppression caused by chemotherapy, which can cause or aggravate a preexisting oligospermia or asthenospermia (e.g., in preexisting varicocele), semen preservation before the treatment is recommended.

#### **29.1.5.4 Stage II Seminoma**

In Stage II (IIA και IIB) low tumor burden disease, the location of the tumor is retroperitoneal and smaller than 5 cm of maximum transversal diameter. The treatment of choice internationally for the most of those patients is irradiation of retroperitoneal lymph nodes, using the «dog leg» technique. As contraindications for applying radiation therapy is the horseshoe kidney anomaly, antecedent radiotherapy for other reasons and inflammatory bowel disease. On the other hand, stage II high tumor burden patients (IIC, bulky disease) are treated with chemotherapy, as the treatment of choice. In particular, usually 3 cycles of BEP are administered while all the necessary precautions are used in order to avoid the risk of tumor lysis syndrome.

#### **29.1.5.5 Stage II Non-seminomas**

Stage II non seminomatous tumors are characterised by ipsilateral tumors in the location of the original tumor, inside or below the renal pelvis and they are usually asymptomatic. In this case, both chemotherapy and retroperitoneal lymph node dissection are reliable options. Patients with extensive disease, with unilateral or bilateral development, usually develop symptoms such as back pain, tumor diameter > 3 cm and increased tumor biomarker level. The likelihood of the disease being surgically unresectable is bigger and systemic chemotherapy is recommended, usually 3 cycles of BEP.

### 29.1.5.6 Stage III

Separating low-risk patients from intermediate and high risk (poor prognosis) population is a critical assessment before administering chemotherapy. The IGCCCG criteria mentioned above are used to determine the risk (Table 29.2). Patients classified as low risk (55% of cases) achieve 5-year survival in a percentage of 92–95%. As this overwhelming cure rate, for case of a metastatic neoplasm, seems difficult to improve further, research efforts in recent years have focused on reducing the toxicity of the required treatment. As a result, the administration of BEP is completed in 3 cycles, instead of 4 and a 3-day regimen is preferred, over the 5-day one, particularly in Europe. In case of contraindication of bleomycin, there is also the alternative of administering EP (cisplatin-ifosfamide) in 4 cycles, in the place of 3 cycles of BEP. The attempts of replacing nephrotoxic cisplatin with better-tolerated carboplatin have failed due to minimizing the survival rates for patients treated with carboplatin. It has to be mentioned that in every study on BEP regimens were conducted the dose of etoposide was 500 mg/m<sup>2</sup> per cycle. Consequently, if a patient is treated with the alternative dose of 360 mg/m<sup>2</sup> (BE<sub>360</sub>P), it is required to incur not less than 4 cycles of treatment.

Patients suffering from stage III intermediate (28%) or poor (16%) prognosis disease, have a less good prognosis, around 80% for the first group and less than 50% for the latter. Those patients are treated with 4 cycles of BEP. Attempts to improve the outcome in this group of testicular cancer patients included the administration of hybrid regimens of alternating chemotherapy combinations (BOP/VIP-B, POMB-ACE), addition of ifosfamide or paclitaxel in the standard BEP regimen (IBEP, T-BEP, TIP) or increase of platinum formulations dose density or intensity. The successful approach of administering high dose carboplatin to some patients with platinum resistant recurrence resulted in the inclusion of carboplatin to various salvation treatment regimens, followed or not by autologous primordial hematopoietic cell transplantation. Until now, it has not been demonstrated by any randomized trial that these approaches are superior to the original BEP regimen, as far as survival rates are concerned. Currently, the most used regimens in first, second and third line treatments are displayed in Table 29.3.

## 29.2 Extragonadal Germ Cell Tumors

Although the majority of germ cell tumors are of gonadal origin, there are cases of neoplasms located outside of the gonads with no identified primary tumor in the genitals. These tumors are originating anywhere in the midline, between the skull (pineal) and the sacrococcygeal region, running an imaginary axis corresponding to

**Table 29.3** The most commonly used chemotherapy regimens in advanced testicular cancer treatment

Regimen (every 3 weeks)	Drug- doses
<b>BE<sub>360</sub>P</b>	Bleomycin 30 IU days 1,8,15
	Etoposide 120 mg/m <sup>2</sup> days 1,2,3
	Cisplatin 50 mg/m <sup>2</sup> days 1,2
<b>BE<sub>500</sub>P 5-days</b>	Bleomycin 30 IU days 1,8,15
	Etoposide 100 mg/m <sup>2</sup> days 1–5
	Cisplatin 20 mg/m <sup>2</sup> days 1–5
<b>BE<sub>500</sub>P 3-days</b>	Bleomycin 30 IU days 1,8,15
	Etoposide 165 mg/m <sup>2</sup> days 1,2,3
	Cisplatin 50 mg/m <sup>2</sup> days 1,2
<b>VIP</b>	Vinblastine 6 mg/m <sup>2</sup> day 1
	Ifosfamide 1,2 g/m <sup>2</sup> days 1–5 + Mesna
	Cisplatin 20 mg/m <sup>2</sup> days 1–5
<b>VeIP</b>	Etoposide 75 mg/m <sup>2</sup> days 1–5
	Ifosfamide 1,2 g/m <sup>2</sup> days 1–5 + Mesna
	Cisplatin 20 mg/m <sup>2</sup> days 1–5
<b>TIP</b>	Paclitaxel 175 mg/m <sup>2</sup> day 1
	Ifosfamide 1,2 g/m <sup>2</sup> days 1–5 + Mesna
	Cisplatin 20 mg/m <sup>2</sup> days 1–5
<b>PG</b>	Paclitaxel 175 mg/m <sup>2</sup> day 1
	Gemcitabine 1250 mg/m <sup>2</sup> days 1,8

the embryonic urogenital bridge. It is believed that those neoplasms are originated from germ cells that remain in locations on the axial skeleton, as a result of their disrupted process of migration during ontogenesis in their early fetal life and consequently their malignant transformation.

Extragonadal tumors are as many as 2–5% of the germ cell tumors in young males and they are usually located in the mediastinum (50–70%), retro peritoneum (30–50%) and epiphysis (<5%), while rarely they have been found in other locations. A special type of extragonadal germ cell tumors is the carcinoma of unknown primary (CUP syndrome) located in the midline with undifferentiated histology, increased plasma biomarkers levels (α-FP, β-HCG, LDH). Although they resemble neoplasms of relevant gonadal histology in terms of morphologic, pathologic, genetic (isochromosoma 12p), biological and pharmacogenomical characteristics (platinum sensitivity) usually appear as non seminomatous tumors (choriocarcinoma, embryonic carcinoma, yolk volume bag) and are characterized by a poor prognosis (5-year survival for 25–30% for primary choriocarcinoma). This explains why the extragonadal germ cell tumors of the mediastinum are classified by default as high-risk (poor prognosis) according to IGCCCG.



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# Chapter 30

## Penile Cancer



Nikolaos Tsoukalas, Konstantinos Tsapakidis, George Kyrgias,  
and Maria Tolia

**Abstract** Penile cancer is a rare tumor. The annual incidence is estimated to be 1 in 100,000 males, accounting for less than 1% of all cancers in men. Regarding histology it consists of squamous cells in 95% of cases. Treatment modalities include surgery, radiotherapy and chemotherapy. Early diagnosis is important since advanced disease is related not only with worse prognosis but also with impaired quality of life.

**Keywords** Penile cancer · HPV · Penis · Cancer · Squamous cell carcinoma

### 30.1 Epidemiology

Penile cancer is a rare malignant disease and an estimated 1100 new cases will be diagnosed each year. The annual incidence is estimated to be 1 in 100,000 males, accounting for less than 1% of all cancers in men [1]. The higher incidence is presented in some areas of South America, Africa, and Asia. The male circumcision seems to be very effective in preventing the development of penile neoplasm [2]. Chronic irritation of the penis from the smegma and urethritis especially when phimosis is coexisting is believed to be the main causative factor of penile cancer. Also, the development of penile cancer has been associated with certain subtypes (in 16 and 18) of the Human Papillomavirus [3, 4].

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## **30.2 Pathology**

### **30.2.1 *Pre-malignant Dermatological Lesions***

Leukoplakia, sclerotic balanitis and giant warts associated with HPV (Buschke-Löwenstein tumors) are classified in this category.

### **30.2.2 *In Situ Carcinoma of the Penis***

Erythroplakia of Queyrat and Bowen disease are included here.

### **30.2.3 *Infiltrating Penile Carcinoma***

Histologically it consists of squamous cells in 95% of the cases, while the remaining 5% can consist of several histologic types, such as sarcoma, melanoma, and rarely basal cell carcinoma to be the most frequent.

## **30.3 Natural History – Clinical Presentation**

The clinical signs in penile cancer vary from a small and usually painless skin damage (ulcerative or exophytic) to extensive damage that can automatically lead to partial amputation of the penis (Fig. 30.1). The predominant sites of the primary lesion are the following: glans penis, prepuce, coronal sulcus and body of penis. The clinical examination should include consideration of the following tumor characteristics: (1) Diameter, (2) Localization, (3) Presence of ulceration, (4) Number of ulcerations, (5) Color, (6) Margins – Mobility of the lesion.

Several patients suffered from phimosis for a long time, while others are complaining of phimosis developed in a short time and this clue should lead us to suspect that penile cancer can be hidden. The patient experiences fear and embarrassment, which probably contributes to delayed diagnosis. Other symptoms may include itching, burning, groin mass and bleeding, and while in those cases where the mass is located close to the external urethral opening, urinary and obstructive symptoms may be present.

The absence of pain in the early stages represents the main reason that explains why patients delay to refer to a physician. In most cases, carcinoma of the penis is characterized by slow locoregional progression. If untreated, it usually grows slowly leading to infiltration of the glans, corpora cavernosa, corpus spongiosum. Finally major bleeding, fistulas, and even urine retention may occur.

The inguinal lymph nodes are the most common site of metastatic spread. The prepuce and the skin of the penis drain to the superficial inguinal lymph nodes,

**Fig. 30.1** Penile cancer

while the glans and the corpora cavernosa to the deep inguinal lymph nodes. Usually, tumours progress slowly at primary and regional sites rather than spread to distant areas. Tumours of the penile urethra spread firstly to the inguinal lymph nodes, whereas those of the bulbomembranous and prostatic urethra metastasize to the pelvic lymph nodes. Approximately one-third of men will present with either clinically or pathologically involved lymph nodes. In 50% of the cases, enlargement of the lymph nodes is often related to inflammatory or infectious processes. Conversely, between 20–40% of patients with clinically negative inguinal lymph nodes have occult metastases [1]. Distant, hematogenous spread is uncommon even in patients with advanced locoregional disease, and usually occurs in the lungs, liver and bones.

### 30.4 Diagnostic Workup

The diagnosis should be confirmed with biopsy of the primary neoplasm. The cytological examination of lymph nodes after fine needle aspiration helps in the differential diagnosis between metastatic and inflammatory lesion [5]. Differential

diagnosis should include venereal disease, urethral stricture, urethral trauma, and urethral polyps. Computed tomography and magnetic resonance imaging is useful in the identification of enlarged pelvic lymph nodes in patients with involved groin lymph nodes. Limited prospective data regarding the use of positron emission tomography with CT are available [6, 7].

### 30.5 Staging

The American Joint Committee on Cancer (AJCC) staging system for carcinoma of the penis 7th Edition (2010) is as follow:

#### Primary Tumor (T)

**Tx** Primary tumor cannot be assessed

**T0** No evidence of primary tumor

**Tis** Carcinoma in situ (Bowen's disease, Queyrat's erythroplakia)

**Ta** Noninvasive verrucous carcinoma

**T1a** Tumor invades sub epithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3–4)

**T1b** Tumor invades sub epithelial connective tissue with lymph vascular invasion or is poorly differentiated

**T2** Tumor invades corpus spongiosum or cavernosum

**T3** Tumor invades urethra

**T4** Tumor invades other adjacent structures (perineum, pubic symphysis)

#### Regional Lymph Nodes (N)

**cNx** Regional lymph nodes cannot be assessed

**cN0** No palpable or visibly enlarged inguinal lymph nodes

**cN1** Palpable mobile unilateral lymph node

**cN2** Palpable mobile multiple or bilateral inguinal lymph nodes

**cN3** Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral

**pNx** Regional lymph nodes cannot be assessed

**pN0** No regional lymph node metastasis

**pN1** Metastasis in a single inguinal lymph node

**pN2** Metastasis in multiple or bilateral inguinal lymph nodes

**pN3** Extra nodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral

#### Distant Metastasis (M)

**M0** No distant metastasis

**M1** Distant metastasis (includes lymph node metastasis outside the true pelvis)

### Stage/Prognostic Groups

<b>0:</b>	Tis N0 M0 Ta N0 M0
<b>I:</b>	T1a N0 M0
<b>II:</b>	T1b N0 M0 T2 N0 M0 T3 N0 M0
<b>IIIa:</b>	T1-3 N1 M0
<b>IIIb:</b>	T1-3 N2 M0
<b>IV:</b>	T4 Any N M0 Any T N3 M0 Any T Any N M1

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science + Business Media.

## 30.6 Prognostic Factors

The main prognostic factors are the extension of the primary tumor and lymph nodal status. The probability of nodal involvement is related to the size, location, and grade of the primary. Invasion of deep-seated structures such as corpora cavernosa is associated with a higher risk of deep inguinal node involvement. Pelvic lymph node involvement is related to a worse prognosis [8].

## 30.7 Treatment

### 30.7.1 Conservative Therapy

Treatment for carcinoma *in situ* and very small tumors includes topical imiquimod and 5 fluorouracil (5-FU). For larger neoplasms, conservative laser surgery or Mohs micrographic surgery can be used.

### 30.7.2 Surgery

Surgical treatment for small tumors may be local excision, such as circumcision or laser therapy. In advanced tumors, operations like penectomy, orchiectomy, scrotoectomy, or cystoprostatectomy are used indicated. Lesions limited to the prepuce may

be managed with circumcision. Lesions on the glans are usually treated by partial penectomy. Larger can be treated by partial or total penectomy. If surgical margins of 2 cm can be achieved, partial penectomy is the procedure of choice. If a clear margin cannot be achieved, total penectomy is warranted [9, 10].

### **30.7.2.1 Surgical Treatment of Inguinal Lymph Nodes**

The morbidity of radical lymphadenectomy and the relative small probability of pathologic involvement of groin nodes have resulted in surveillance as the initial management of regional lymph nodes in clinically negative cases at some centres [11, 12]. Lymph node dissection is associated with complications like wound dehiscence, infection, lymphocele, chronic lymphedema, or venous thromboembolism. Sentinel node biopsy represents as a less morbid method of evaluating inguinal nodes [13]. An extended pelvic nodal dissection is justified in patients with evidence of inguinal involvement (positive biopsy of Cloquet's node) that they may be at risk for microscopic metastases. Patients with clinically negative lymph nodes (stage I disease and well-differentiated histology) may benefit from elective irradiation to the inguinal lymph nodes.

### **30.7.3 Chemotherapy**

The cornerstone of chemotherapy combinations for advanced penile cancer is cisplatin. There are trials with cisplatin-based combinations that showed response rates of 15–55% and overall survival of 5–12 months [14, 15]. The chemotherapy combinations that have been studied include bleomycin-methotrexate-cisplatin, cisplatin-5-fluorouracil, cisplatin-irinotecan and paclitaxel [16]. Before any treatment it should be taken into account all the possible toxicities of these chemotherapy combinations. In some cases with initially unresectable disease chemotherapy can be administered as neoadjuvant treatment. In particular, in patients with fixed, multiple or bulky nodes (more than 4 cm) we can try to increase the respectability of the disease with a neoadjuvant approach. One chemotherapy combination that has been studied in this setting was ifosfamide-paclitaxel-cisplatin and the response rate was around 50% while 73% of patients managed to undergo surgery at the end [17]. In future, more clinical trials not only with classical chemotherapy but also with novel targeted agents may demonstrate better outcomes for patients with advanced penile cancer.

## **30.8 Radiation Therapy**

Radical Radiotherapy (external beam or interstitial brachytherapy) is effective in achieving loco-regional control.



### 30.8.1 External Beam Radiation Therapy

The primary advantage of megavoltage EBRT is penis preservation. If indicated, circumcision must be performed before the start of EBRT, in order to minimize radiation-induced toxicity. A smaller daily fraction size (1.8–2.0 Gy) and a higher total dose (60–65 Gy with the last 5–10 Gy delivered as a boost) are preferable to avoid soft tissue fibrosis and necrosis [1].

EBRT for clinically negative inguinal lymph nodes represents an important component of optimal therapeutic management of microscopic tumor spread. More than 20% of patients will develop metastatic nodes. If clinical and radiographic confirms a N0 disease, the dose to these nodes may be limited to 50 Gy. Grossly metastatic nodes can be removed surgically either before or after inguinal EBRT. Postoperative EBRT to both groins contributes to increase loco regional tumor control. The irradiated area should include inguinal, external and internal iliac lymph nodes. In palpable lymph nodes, doses of approximately 70–75 Gy/1.8–2.0 Gy per fraction with reducing fields (after 50 Gy) should be considered [1].

Langsenlehner T et al. [18] assessed retrospectively the outcome of 24 patients treated with adjuvant EBRT (n = 22) and 192Ir high-dose-rate BT (n = 2) following total penectomy (n = 7), partial penectomy (n = 10), or local excision (n = 7). In 14 patients, irradiation was delivered after incomplete tumor resection. In 20 cases the planning target volume (PTV) included the regional lymph nodes. Median total dose of EBRT was 56 Gy/1.8–2 Gy (range, 50–60 Gy). BT was given with a total dose of 45 Gy/3 Gy. EBRT was a successful modality of treatment in terms of organ preservation and LC after microscopically incomplete operation. EBRT of the regional lymph nodes was considered in case of high-risk features and following excision of extensive lymph node involvement. The 5 year LC rate was 74.8%, the 5 year metastases-free survival and PFS rates were 86.7% and 64.5%, respectively. The 5 year CSS and OS rates were 84.3 and 56.6%, respectively.

Johnson TV et al. [19, 20] queried 17 SEER (Surveillance, Epidemiology, and End Results) registries and they found that high grade ( $p < .001$ ), T classification ( $p = .010$ ), and adjuvant EBRT ( $p = .004$ ) were significant predictors of OS. In particular, EBRT after lymphadenectomy was associated with increased OS (HR, 0.58; 95% CI, 0.41–0.84).

Burt LM et al. [21] evaluated the stage distribution and outcomes for radiotherapy and surgery in a U.S. population database. By multivariable analysis grade 2–3, T3 stage, and metastatic lymph nodes were adverse prognostic factors for CSS. The authors concluded that adjuvant chemo radiation to the inguinal LN and pelvis should be strongly considered for any node positive patient after lymphadenectomy. Even if improved OS or CSS is not achieved with adjuvant EBRT, there may still be benefit of its use in reducing local failures (LF) and the concomitant morbidity of failing to achieve LC within the pelvis and groin.

As in squamous tumors of other sites that drain to the inguinal regions, patients with multiple positive nodes or extra capsular spread should be offered postoperative EBRT [22].

### 30.8.2 Brachytherapy

Brachytherapy (BT) may be an alternative, effective and conservative treatment modality to amputation for T1 and T2 tumors <4 cm in size, located on the glans [23].

Delaunay et al. [24] evaluated the oncologic outcomes, sexual function, and the sexual behavior of 47 patients treated by BT (192Ir) for cancer of the penis. The authors investigated into their sexuality by means of a questionnaire and found that BT had a moderated impact on the sexual functions and the sexual behavior of the patients. The specific survival and the disease-free survival at 5 years was 87.6% and 84%, respectively. 66% of the patients preserved their penis, 58.8% remained sexually active after treatment and 94.4% had erections after treatment. The main predictive factor was age.

De Crevoisier R et al. [23] analyzed the results of interstitial low-dose-rate BT for squamous cell carcinoma, confined to the glans in a total of 144 patients. Inguinal nodal dissection was performed in 19% of patients (all N negative). After circumcision, BT was performed using the hypodermic needle technique. Median iridium length per patient was 24 cm (range, 4–108) and median dose was 65 Gy (range, 37–75). Median treated volume was 22 cm<sup>3</sup> (range, 5–110) and median reference isodose rate was 0.4 Gy/h (range, 0.2–1.2). With a median follow-up of 5.7 years, the 10 year penile recurrence, inguinal lymph node recurrence, and inguinal nodal metastasis rates were 20%, 11%, and 6%, respectively. The 10-year probability of avoiding penile surgery (for complications or local recurrence) was 72% and the cancer-specific survival rate was 92%. Diameter of tumor was a risk factor of recurrence ( $p = 0.02$ ). Salvage local treatment was effective. Delayed complications included stenosis, necrosis, fibrosis and ulceration. The 10-year painful ulceration and stenosis risk rates were 26% and 29%, respectively. Seven patients required excision for necrosis. Treated volume and reference isodose rate significantly increased the risk of complications and dose rate should be limited to decrease toxicity.

Hasan S *et al* [25] presented a meta-analysis from the American Brachytherapy Society, comparing the overall survival (OS) and local control (LC) rates between penectomy and brachytherapy. 19 retrospective studies were published between the years 1984–2012, and detailed OS and LC were collected. A total of 2178 patients, with a median age of 61 years were included (Surgery: 1505, BT: 673). The BT arm included high dose rate, low dose rate, and pulse dose rate between 50 and 70 Gy (median 65), with or without adjuvant EBRT, chemotherapy, or lymph node dissection. Penectomy with adjuvant EBRT was included in the surgery group, and EBRT with a brachytherapy boost was included in the BT group. While penectomy provided better control (5-year LC rate of 84% vs. 79% with BT), there was no survival benefit (5 year OS with BT was 73% vs. 76% with surgery). In early stage tumors there was no survival or control difference. Among the surgery patients in a Stage I/II, the 5 year OS and LC was 80% and 86%, respectively. Of the 209 early stage patients who received brachytherapy, the 5-year OS was 79% and LC was 84%. Chi-square testing demonstrated no difference for either OS or LC for an early stage disease. The organ preservation rate for BT treatment was 74%. In most cases failed brachytherapy could be salvaged with surgery.

### 30.9 Program for Follow Up of Patients with Penile Cancer

Most relapses occur in the first 2 years after initial treatment and the early detection of lymph node metastases is of particular value. Monitoring includes clinical examination, chest radiograph and abdominal CT scan. Thus, depending on the initial disease management, the guidelines of the European Association of Urology suggest the following patient monitoring program:

1. Conservative treatment: Examination every 2 months the first and second year, every 3 months the third year and every 6 months the fourth-fifth year.
2. Partial or total penectomy: Examination every 4 months in the first and second year, every 6 months the third year and each time the fourth-fifth year.
3. After lymphadenectomy with negative (–) lymph nodes examination should be held every 4 months the first year and every 6 months the second year and then is not necessary.
4. After lymphadenectomy with (+) lymph nodes examination should be held according to the protocol of the hospital.
5. In conclusion penile carcinoma is one of the few tumors, that lymphadenectomy offers high cure rates even when infiltrated lymph nodes already exist when diagnosed. The pattern and the intervals of follow up are directly related to the initial treatment of the primary tumor and regional lymph node metastases.

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# Chapter 31

## Squamous Cell Carcinoma of the Head and Neck



**Emmanuel Seront, Jean-Pascal Machiels, and Sandra Schmitz**

**Abstract** Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most common cancer worldwide. The main risk factors for cancers of the oral cavity, larynx, oropharynx, and hypopharynx are alcohol and tobacco abuse. In addition, the human papillomavirus is another established cause of oropharyngeal cancer. The treatment for early-stage squamous cell cancers of the head and neck includes generally only one treatment modality, either surgery or radiotherapy. The treatment for locally advanced head and neck cancers is multimodal, with either definitive chemoradiation or surgery followed by adjuvant radiation or chemoradiation as indicated by pathologic features. However, despite this aggressive multimodal treatment, 40–60% of the patients will relapse, highlighting the importance to improve our initial local control. For recurrent and/or metastatic disease, systemic agent is indicated, including chemotherapy, biological agents and immune checkpoint inhibitors. This chapter describes the molecular pathogenic pathways implicated in HNSCC development as well as its general management.

**Keywords** Head and neck cancer · Radiotherapy · Cetuximab · Immune checkpoint inhibitors · Human papilloma virus

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## Abbreviations

CRT	Chemoradiotherapy
CT	Computed Tomography
DW-MRI	Diffusionweighted MR
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
IHC	Immunohistochemistry
IMRT	Intensity Modulated Radiotherapy
LA-HNSCCC	Locally advanced Head and neck Squamous cell carcinoma
LRC	Locoregional control
MRI	Magnetic Resonance Imaging
ND	Neck Dissection
ORR	Overall response rate
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
RT	Radiotherapy

## 31.1 Introduction

Head and neck cancer (HNC) is a broad term that encompasses a large number of tumour entities originating from different subsites, such as the nasal cavity, nasopharynx, oral cavity, oropharynx, larynx, hypopharynx and salivary glands. By far, head and neck squamous cell carcinoma (HNSCC) is the most common histological subtype [1].

The treatment choice depends on the location of the primary tumor, the stage of the disease, and the expected oncological and functional outcomes. Early stage HNSCC is usually treated with one single treatment modality (surgery or radiotherapy). However, approximately 60–80% of HNSCC patients present with locoregionally advanced disease at time of diagnosis and the main treatment options are (chemo-) radiotherapy and surgery.

## 31.2 Epidemiology

### 31.2.1 Incidence and Prevalence

With approximately 742,270 new cases and 407,037 deaths worldwide for the year 2015, HNC is the sixth most common cancer worldwide. Approximately 90% of all HNCs are (HNSCC). In the United States, more than 54,000 new cases were

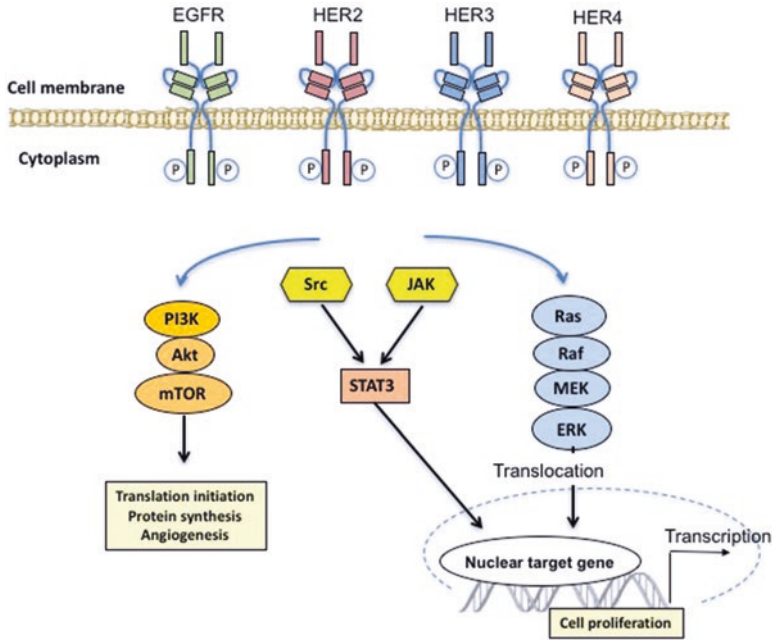
diagnosed in 2014, resulting in an annual incidence of 15 per 100,000, with 12,000 deaths attributed to the disease. In Europe, HNSCC incidence and mortality rates are higher, with approximately 140,000 new cases diagnosed in 2014, corresponding to an annual incidence of 43/100,000. Male to female ratio ranges from 2:1 to 4:1 and the median age at diagnosis is in the sixth decade of life. In Europe, the relative survival rate for HNC patients is 72% at 1 year and 42% at 5 years in adults [1].

### **31.2.2 Risk Factors**

Tobacco use and alcohol are the two most important risk factors for the development of HNSCC and act synergistically. Some components of tobacco (benzopyrene) and of alcohol (acetaldehyde) induce DNA structural damage and genetic variations of systems implicated in DNA damage correction (nucleotide excision repair system or the base excision repair system). Enzymes dedicated to metabolize these toxins (cytochrome P450) play a role in individual sensitivity to these carcinogens. Compared to non-smokers, tobacco users have a 4–5-fold increased risk for cancer in the oral cavity, oropharynx and hypopharynx and a ten-fold increased risk of laryngeal cancer. HPV is a well-established independent risk factor, accounting for 20 to 60% of oropharyngeal cancer [2]. High-risk HPVs include types 16, 18, 31 and 33, with HPV type 16 accounting for over 90% of HPV-positive oropharyngeal cancer. HPV-positive HNSCC differs demographically, molecularly, and clinically from HPV-negative tumors. Clinically, HPV-positive oropharyngeal cancer patients are younger, have a better performance status, consume less alcohol and tobacco, have more sexual partners and frequently present with a smaller primary tumor associated with multiple cystic cervical lymph nodes. HPV-associated oropharyngeal cancer is associated with a favorable prognosis, compared to HPV-negative tumors. In North America, 56% of oropharyngeal HNSCC are HPV-positive, followed by 52% in Japan, 45% in Australia, 39% in northern and western Europe, and 13% in the rest of the world [3–5]. The signification of HPV infection in other subsites than oropharynx is unknown and controversial.

## **31.3 Molecular Mechanisms**

The Epidermal Growth Factor Receptor (EGFR) is a member of the transmembrane tyrosine kinase Human Epidermal Receptor (HER) family, which includes also HER2 (ErbB2), ErbB3 and ErbB4. Binding of ligands to EGFR results in its homo- or heterodimerization with other HER receptors, subsequent autophosphorylation and activation of downstream signaling cascades including Ras/Raf/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of Rapamycin (mTOR), and Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathways (Fig. 31.1). EGFR or transforming



**Fig. 31.1** HER family and subsequent activation of different signaling pathways involved

growth factor alpha (TGF- $\alpha$ ) overexpression is an early marker of HNSCC carcinogenesis [6]. EGFR overexpression is observed in 90% of HNSCC and results mainly of increased mRNA synthesis and to a minor extent, *EGFR* amplification (10–30%). *EGFR* activating mutations are rare in HNSCC (1–7%) [7, 8]. EGFR overexpression and a high number of *EGFR* gene copy number are associated with poor prognosis [9]. PI3K/Akt/mTOR pathway activation may arise by several mechanisms, including loss of the phosphatase and tensin homolog tumor suppressor (PTEN) protein in 10% of HNSCC and amplification of the catalytic subunit of PI-3-kinase in 37% of HNSCC tumors. Activating *H-RAS* mutations have been found in 4–5% of HNSCC cases and result in MAPK pathway sustained activation [10, 11]. The JAK/STAT cascade mediates EGFR signaling; the recruitment of STAT3 by JAK to the activated EGFR leads to STAT3 translocation to the nucleus where STAT3 promotes cell proliferation, apoptosis suppression and angiogenesis. STAT3 is constitutively activated and overexpressed in a majority of patients with HNSCC. High levels of activated STAT3 correlate with advanced tumor stage and poor patient prognosis [13]. *MET* overexpression is observed in 80% of HNSCC and increased *MET* copy numbers in 13%. *MET* expression is associated with reduced disease-free and overall survival in HPV-negative HNSCC and has been associated with resistance to radiation, cisplatin and cetuximab [12]. Activation of the transmembrane receptor NOTCH1 by ligands leads to nuclear translocation of NOTCH1 intracellular domain to promote transcription of genes implicated in survival.

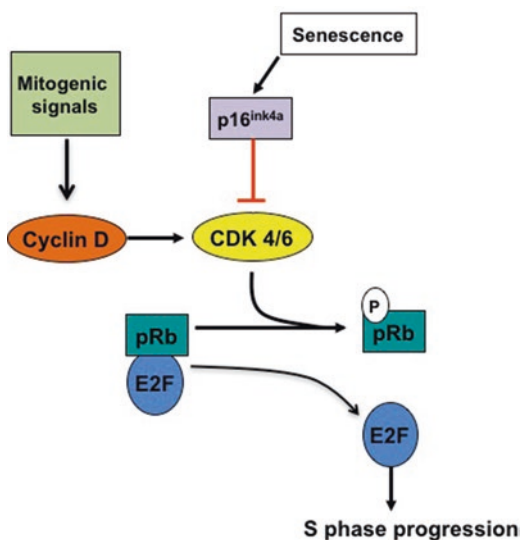


*NOTCH1* gene mutation is reported in 14–15% of HNSCC; majority are nonsense mutations, resulting in loss of the transcriptional activation domains, therefore suggesting a tumor-suppressor role in HNSCC [14].

The tumor suppressor proteins p53 and pRb are implicated in the cell cycle regulation. In response to DNA damage, p53, encoded by *TP53* mapped on chromosome 17p13, arrests the cell cycle and activates repair or initiate apoptosis. HNSCC appears the most common p53 mutation-carrying cancer, with *TP53* mutation reported in 50–80%. *TP53* mutation is associated with tobacco and alcohol use in HNSCC and is predictive of resistance to treatment and poor prognosis. pRb binds and inhibits E2F, a transcription factors that promotes S-phase transition. Mitogenic signals activate the complex cyclin D1–cyclin dependent kinase 4/6 (CDK4/6) that phosphorylate pRb, resulting in the release of E2F. The cyclin D1-CDK4/6 complex is inhibited by p16INK4A, encoded by *CDKN2A*, and by the cyclin-dependent kinase inhibitor 1 (CDKN1). pRb is targeted early in the carcinogenesis of HNSCC through *CDKN2A* inactivation occurring in the majority of HPV-negative HNSCC patient. *CCND1* encodes cyclin D1 and is also amplified or overexpressed in over 30% of HPV-negative HNSCC [15–17] (Fig. 31.2).

HPV promotes carcinogenesis by interfering with cell cycle regulation. The E6 viral protein promotes rapid degradation of p53 via the ubiquitin–proteosome pathway and the E7 viral protein competes with E2F transcription factor for binding to the pRb tumour suppressor, promoting *in fine* cellular proliferation. Loss of p16 expression is common in HPV-negative HNSCC. By contrast, in HPV-positive tumors, p16 is overexpressed due to the loss of negative feedback induced by inactivation of Rb by E7 [18, 19]. The Cancer Genome Atlas Network reported the results of whole-genome sequencing on tumor tissue from 279 patients with HPV-positive and HPV- negative HNSCC [20]. These data confirm the nearly universal

**Fig. 31.2** Mitogenic signals activate the complex cyclin D1–cyclin dependent kinase 4/6 (CDK4/6) that phosphorylate pRb, resulting in the release of E2F. The cyclin D1-CDK4/6 complex is inhibited by p16<sup>INK4A</sup>, encoded by *CDKN2A*



loss of function of p53 and *CDKN2A* gene inactivation in HPV-negative HNSCC. HPV-positive HNSCCs are characterized by wild-type *TP53* and *CDKN2A*. The most frequent gene alteration in HPV-positive HNSCC is in the *PIK3CA* gene.

### 31.4 Diagnosis and Staging

The clinical presentation varies with the site of origin; the most common symptom is chronic sore throat for pharynx tumors and hoarseness and voice loss for laryngeal tumors. Typically, pain is unilateral with or without referred otalgia. A unilateral asymptomatic mass in the neck could be an initial symptom. At initial presentation, over 40% of patients have regional nodal involvement and 10% present with distant metastases.

Flexible fiberoptic endoscopy allows assessment of the tumor size and extension to adjacent structures, such as vocal cord. A rigid endoscopy under general anesthesia remains a major step in the diagnosis to accurately delineate tumor extension and perform deep biopsies. All upper aerodigestive tract must be meticulously assessed in order to exclude other synchronous primaries.

CT scan and/or MRI are essential to assess the localisation and extension of the primary tumor and regional lymph nodes. MRI tends to be superior to CT for tumors of the oral cavity and oropharynx and to predict local tumor invasion. Both modalities achieve 80%-rate accuracy in the evaluation of lymph nodes, when using a cut-off value at 10 mm (short axis diameter) [21, 22]. Diffusion-weighted MRI (DW-MRI) was reported as a better tool for regional staging of HNSCC and should be used routinely in the initial imaging work-up [23]. Even if its accuracy seems not superior to that of CT or MRI for nodal staging, 18F-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) improves the detection of distant metastases and is also a valuable tool to predict neck node negativity 12 weeks after chemoradiation with a negative predictive value for assessment of response of 98.7% for the primary tumor and 99% for the neck [24–26].

HNSCC should be staged according to the TNM system; the recently published eighth edition TNM classification institutes major changes to the previous staging system of HNSCC. Modifications were made about new stage classifications in HPV-related oropharyngeal cancers, T and N classification for nasopharyngeal cancer, T categories for oral cavity squamous cell carcinomas, N categories for non-viral related head and neck cancer and unknown primary [27]. A multidisciplinary treatment schedule should be established in all cases. The patient's nutritional status must be corrected and maintained. Dental rehabilitation is indicated before radiotherapy.

## 31.5 Pathology

Pathological diagnosis should be made according the World Health Organization classification from a surgical biopsy. HNSCC accounts for 90–95% of the lesions of the upper aerodigestive tract. Less common histologies include cancer from minor salivary gland like adenocarcinoma, adenoid cystic carcinoma and mucoepidermoid carcinomas. SCC is characterized by invasive growth and evidence of squamous differentiation. SCC is traditionally graded into well-, moderately- and poorly differentiated, based on nuclear pleomorphism, mitotic activity and degree of differentiation. Prognostic factors include surgical resection margins, localization and depth of the tumor and presence of extracapsular spread in lymph nodes metastases.

HPV is pathogenetically linked to SCC of the oropharynx, particularly of the palatine and lingual tonsils. Even if the gold standard for HPV detection remains in situ hybridization or detection of E6/E7 mRNA by reverse transcriptase polymerase chain reaction, immunohistochemical (IHC) analysis of the tumor tissue for p16<sup>INK4A</sup> is now used in the head and neck community as the initial test of choice and a surrogate marker to identify high-risk HPV infection. In oropharyngeal SCC, sensitivity of p16 IHC approaches 100% with a specificity around 80% [28]. The stratification of oropharyngeal cancers by HPV status has important clinical implications, as patients with HPV-positive HNSCC patients, especially oropharyngeal SCC, have better overall survival (OS), disease free survival (DFS) and locoregional control (LRC) compared to the HPV – negative patients, independently of the treatment modality [29–33]. In a study, HPV-positivity was associated with a better 3-year OS (83.4% vs. 57.1%) and a 58% reduction of risk of death (HR = 0.4; 95% CI 0.27–0.66) compared to HPV-negativity in patients treated with (chemo)radiotherapy [34].

## 31.6 Treatment Approaches

The therapeutic strategy requires consideration of tumor's localization and extension, age, performance status and the anticipated functional outcome and long-term toxicity.

Limited or early-stage disease is the presenting stage in approximately 40% of patients and is usually treated with surgery or radiation alone; surgery and radiotherapy showed similar locoregional control (LRC), based on non-randomized retrospective studies.

Approximately 60–80% of HNSCC patients present with loco-regionally advanced disease (LA-HNSCC) at time of diagnosis. One of the treatment options is surgery plus postoperative RT and, for high-risk patients (nodal extracapsular extension and/or R1 resection), post-operative chemoradiotherapy (CRT). However,

even in resectable patients, when the anticipated functional outcome and/or the prognosis is so poor that mutilating surgery is not justified, radical CRT is preferred.

The treatment of p16-positive oropharyngeal cancer is similar to p16-negative HNSCC. Due to a better prognosis, de-escalating strategies are under investigation in HPV-positive oropharyngeal cancer but are not a standard of care today.

### ***31.6.1 Locoregional Therapy***

#### **31.6.1.1 Surgery**

Primary curative surgery remains the best primary treatment for a majority of localized early stage HNC and is reserved for resectable tumors in which clear margins can be achieved and function can be preserved [28].

For small transorally accessible cancers of the oral cavity, pharynx, and larynx, surgical excision can be achieved with functional preservation of the involved organ and good oncological results. Other modalities including the concept of minimally invasive surgery could also be employed depending on the anatomy and tumor characteristics. Regarding oropharynx, transoral approaches including transoral laser microsurgery and robotic surgery have shown improved functional outcomes and similar oncologic outcomes to primary radiation. For locally advanced laryngeal cancer, good long-term oncological outcome with laser microsurgery was recently reported. These techniques could be associated, in experienced hands, with less morbidity than traditional open surgery [35–37]. The development of chemoradiation has changed the role of surgery for LA-SCCHN, in particular when a voice-sparing surgical approach is not possible [38]. Today, the surgeon is more frequently faced with failures of primary non-surgical therapies. Advances in microvascularized free flaps have expanded the possibilities of reconstruction following resection of advanced tumors and improves the cosmetic and the functional outcome. Selection of patients is important in salvage surgery, as tumor invading the common carotid artery, base of the skull or the prevertebral muscles should be considered unresectable [39]. When surgery is the primary treatment, neck dissection is recommended in most tumors with the exception of early tumors of the vocal cord. The rationale for a selective neck dissection is based on known patterns of metastases from each site; the risk of occult lymph node metastases in patients clinically N0 is around 30% [40]. Typically, unilateral or bilateral dissection of levels II, III and IV is indicated in oropharynx cancer. Neck dissection is also recommended in patients treated with primary chemoradiation, when residual disease is suspected 12 weeks after the end of chemoradiation [41–43].

### 31.6.1.2 Radiotherapy and Concomitant Chemoradiation

In LA-HNSCC, RT is effective both as a primary modality concurrently with chemotherapy and as an adjuvant to surgical treatment following surgery. The dose of radiation for HNSCC varies from 60 Gy to 70 Gy, depending on timing of treatment and adjuvant vs definitive initial treatment.

Besides the treatment of the primary tumor itself, elective lymph node irradiation by external beam RT is necessary in the eradication of subclinical disease.

Concomitant platinum-based CRT is the standard of care in LA-SCCHN, in non-resectable patients but also in resectable patients when the anticipated functional outcome and/or the prognosis is so poor that mutilating surgery is not justified. The updated meta-analysis of chemotherapy in combination with RT for HNSCC (MACH-NC) showed that the addition of chemotherapy concomitantly to RT improves the absolute 5-year survival by 6.5% [44, 45]. High-dose cisplatin (100 mg/m<sup>2</sup> day 1, 22 and 43) remains the standard radiosensitizer in the treatment of HNSCC. The role of induction CT with docetaxel, cisplatin and 5-fluorouracil is controversial as it failed to demonstrate a statistically significant difference in OS and PFS compared to CRT alone [46, 47]. However for larynx preservation, induction chemotherapy and concomitant CRT give similar long-term survival even if concomitant CRT improves the rates of larynx preservation and local control at 5 and 10 years compared with induction therapy or RT alone [38].

Cetuximab combined with RT therapy improves the duration of locoregional recurrence-free survival (24.4 vs 14 months;  $P = 0.005$ ) and OS (49 vs 29.3 months;  $P = 0.03$ ) compared to RT alone, apparently without increasing the radiation-induced side effects [48]. Cetuximab-RT is therefore considered an alternative to CRT, however, so far there are no data comparing CRT with cetuximab-RT.

To minimize toxicity following radiotherapy for HNSCC, there is a shift away from the more simple RT techniques towards more advanced RT. By varying the beam intensity across shaped radiation fields, Intensity-modulated radiotherapy (IMRT) holds the promise to reduce radiation dose to organs at risk, such as the parotid glands, potentially reducing xerostomia. Randomized trials showed that IMRT significantly reduces the incidence of xerostomia and improves quality of life without jeopardizing LRC and OS [49]. IMRT is therefore standard of care in HNSCC.

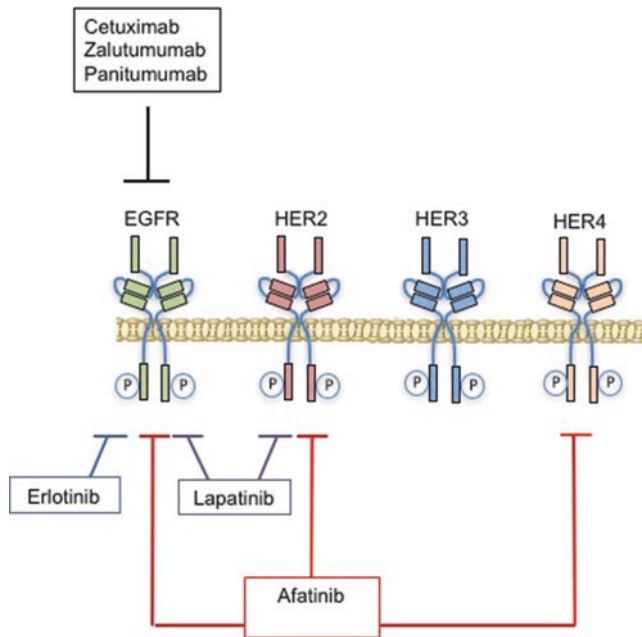
### 31.6.2 Systemic Therapy (*Incurable Recurrent and/Ormetastatic Disease*)

Cetuximab is a chimeric mouse-human IgG1 monoclonal antibody (mAb) that binds EGFR extracellular domain, preventing its ligand-mediated activation. The combination cetuximab and platinum-based chemotherapy is the standard frontline treatment of recurrent or metastatic (R/M) HNSCC, improving overall response rate

(ORR), progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone. In the phase III EXTREME trial, 442 patients with R/M SCCHN were randomized to receive chemotherapy (cisplatin or carboplatin plus 5-Fluorouracil) alone or in combination with cetuximab as a first-line palliative regimen. Patients may have previously received platinum chemotherapy in the LA-HNSCC setting if  $\geq 6$  months before randomization. In the experimental arm, patients with at least stable disease after six cycles of chemotherapy received weekly cetuximab monotherapy until progression disease. Cetuximab improved the primary endpoint median OS from 7.4 to 10.1 months ( $P = 0.04$ ), median PFS from 3.3 to 5.6 months ( $P < 0.001$ ) and ORR from 20% to 36% ( $P < 0.01$ ). Cetuximab was well tolerated and did not impair quality of life [50]. Retrospective biomarker analysis showed no predictive correlation between *EGFR* amplification, p16 or HPV status and cetuximab efficacy [51]. Association of cetuximab with other regimens such as docetaxel and cisplatin showed promising results in R/M HNSCC patients in first-line setting, with an ORR reaching 44.4%, a median PFS of 6.2 months and a median OS of 14 months [52]. However, further studies are needed to compare this regimen to the EXTREME regimen. Cetuximab monotherapy showed also efficacy in second-line setting after failure of platinum-based therapy, based on pooled results of 3 phase II trials that showed an ORR reaching 10–13%, and a median OS between 4.3–6.1 months. As these results seem superior to historical second-line agents, and despite randomized trial, cetuximab monotherapy was approved by the Food and Drug Administration (FDA) in R/M disease after failure of platinum-based chemotherapy [53].

Benefit observed with cetuximab appears however moderate and resistance occurs rapidly. Panitumumab, a fully human IgG2 mAb was evaluated in first-line setting in R/M HNSCC in a similar design than EXTREME trial but did not improve significantly OS compared to chemotherapy (11.1 vs 9.0 months, respectively;  $P = 0.14$ ) [54]. Panitumumab was also evaluated as second-line monotherapy (PRISM trial) but showed also limited activity [55], which is probably explained by the antibody-dependent cellular cytotoxicity (ADCC) induced by cetuximab, which potentially enhances its antitumor activity. Other anti-EGFR agents such as the IgG1 mAb zalutumumab and the small tyrosine kinase inhibitor erlotinib and gefitinib showed modest efficacy in R/M HNSCC [56]. Targeting multiple tyrosine kinase receptors is of particular interest but the clinical results observed with lapatinib (EGFR and HER2 inhibitor) [57] and with afatinib (EGFR, HER2 and HER4 inhibitor) show limited activity in R/M HNSCC [58] (Fig. 31.3). However, biomarker analysis could help to identify the best candidates for these targeted therapies. For example, a propensity for greater PFS benefit with afatinib than methotrexate was observed in patients with p16-negative, PTEN-high, HER3-low, and EGFR-amplified disease [58]. This however requires biomarker-guided randomized trials.

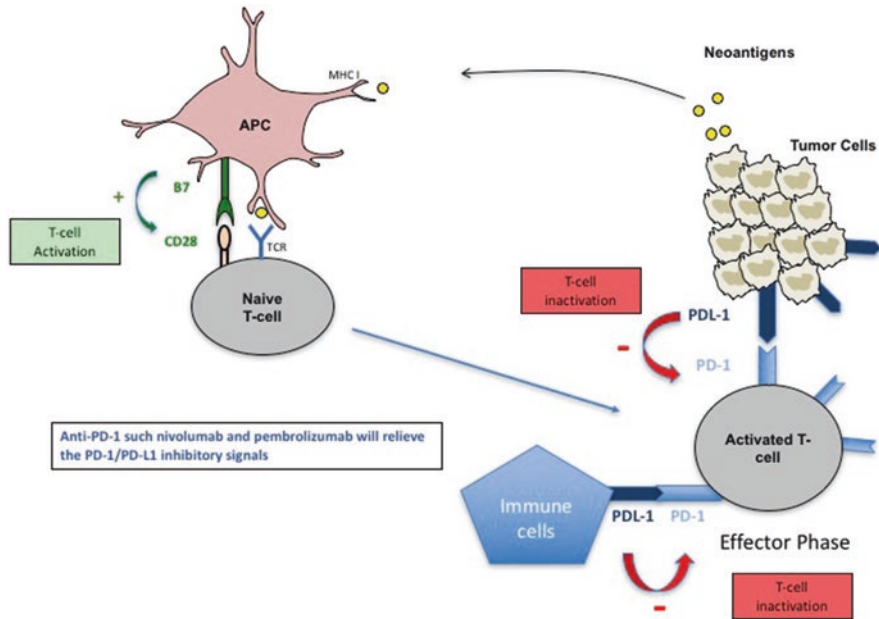
Immune checkpoint inhibitors (ICI) appear as a new treatment standard in R/M HNSCC. HNSCC tumors express multiple immune checkpoint molecules that are implicated in decreased antitumor immunity. Binding of the immune checkpoint Programmed death-1 (PD-1) expressed on activated T-cell to its ligand PD-L1,



**Fig. 31.3** Agents targeting EGFR and other tyrosine kinase receptors

which is expressed on tumor cells and tumor-infiltrating immune cells, lead to a decrease of T-cell activity (Fig. 31.4). Pembrolizumab and nivolumab are two ICI that, by targeting PD-1, reactivate the immune response of T cells to the tumor. In the phase III trial CheckMate 141, nivolumab improved survival in R/M HNSCC patients who progressed within 6 months after platinum-based chemotherapy. Nivolumab monotherapy yielded superior OS over standard therapy (methotrexate, docetaxel, or cetuximab) with a median OS of 7.5 months compared to 5.1 months ( $P = 0.01$ ) and a 1 year OS rate of 36% compared to 16.6%, respectively. ORR was 13.3% with nivolumab vs 5.8% with standard therapy. Somewhat higher tumor responses and survival were seen in patients with tumor expressing PD-L1 even though some patients with PD-L1-negative tumors presented also a benefit from anti-PD1 inhibitors [60]. This led to FDA approval of nivolumab in R/M HNSCC after failure of platinum-based therapy.

Pembrolizumab seems also superior to standard treatments for R/M HNSCC. Although not significant, in the randomized phase III Keynote-040 trial, pembrolizumab showed a survival benefit (primary endpoint) over standard treatment (methotrexate, docetaxel or cetuximab) with a median OS of 8.4 compared to 7.1 months ( $P = .02$ ). The magnitude of OS benefit was greater in patients with PD-L1 expressing tumors [61]. Statistical significance was not reached and this study was considered as negative; however, these results are concordant with those observed with nivolumab, confirming indirectly the benefit of pembrolizumab in HNSCC. Furthermore, pembrolizumab and nivolumab present a better toxicity



**Fig. 31.4** Tumor cells neoantigens, which are captured by antigen-presenting cells (APC). APC migrate to lymphoid organs, where they activate naive T cells, through binding of stimulatory molecules (B7 and CD28). Activated T-cells in turn infiltrate tumors and kill cancer cells. However, in cancer, **immune checkpoints** can downregulate the anti-tumor immunity. PD-1 is an inhibitory receptor expressed on activated T-cells. When binding to PD-1, PD-L1 expressed on tumor cells and immune cells transmits an inhibitory signal to activated T-cells, resulting in the suppression of T-cell activity. By targeting PD-1, Nivolumab and pembrolizumab can reactivate the T-cell activity

profile over standard therapies and improvement in quality of life. Currently, nivolumab and pembrolizumab present an efficacious therapeutic option for R/M SCCHN patients who progressed after platinum-based therapy, regardless of PD-L1 expression.

Results of these different trials are presented in Table 31.1.

## 31.7 Future Developments and Conclusions

Despite multimodal treatment including surgery and/or radiation therapy and/or chemotherapy, 40 to 60% of the patients with LA-HNSCC will relapse, highlighting the importance to improve our local control. Improvement in technology including imaging, radiation technique, and surgery has allowed better functional and cancer outcomes. Ongoing trials address important questions regarding the role of new molecular imaging with new tracers ([<sup>18</sup>F]-fluorothymidine (FLT) and



**Table 31.1** Selected trials in R/M HNSCC

Trial	Design	Disease stage	N	Regimens	Response rate or duration	Median PFS	Median OS	Toxicity and predictive factors
EXTREME [49]	Randomized phase III	R/M HNSCC First-line setting	220 222	Platinum-5FU Platinum-5FU + cetuximab	NA	3.3 mths* 5.6 mths	7.4 mths* 10.1 mths	No effect of p16 expression
GORTEC study [51]	Single-arm phase II	R/M HNSCC First-line setting	54	Docetaxel + cisplatin + cetuximab	ORR: 44.4%	6.2 mths	14 mths	Grade 3/4 rash 16.6%
Baselga [52]	Single-arm phase II	R/M HNSCC Platinum-resistant	96	Platinum-based CT + cetuximab	ORR: 10%, SD: 43%	85 days	183 days	NA
Herbst [52]	Single-arm phase II	R/M HNSCC Pts progressing after first line CT	25 54	2x 3-week ciplatin CT in first line If PD: Cisplatin + cetuximab (n = 25) PD2 pts. = PD pts. within 90 days after CT (n = 54)	ORR PD1: 20% ORR PD2: 6%	PD1: 3 mths PD2: 2 mths	PD1: 6.1 mths PD2: 4.3 mths	NA
Vermorken [52]	Single-arm phase II	R/M HNSCC Platinum-resistant	103	Cetuximab	ORR: 13%	TTP: 70%	178 days	NA
SPECTRUM [53]	Randomized phase III	R/M HNSCC First-line setting	330 327	Cisplatin-5FU Cisplatin-5FU + Panitumumab	NA	4.6 mths* 5.8 mths*	9 mths 11.1 mths	Grade ≥ 3 AEs more frequent with panitumumab; Better OS and PFS in p16- pts
PRISM [54]	Single-arm phase II	R/M HNSCC Platinum-resistant	51	Panitumumab	ORR: 4%	1.4 mth	5.1 mths	NA

(continued)

**Table 31.1** (continued)

Trial	Design	Disease stage	N	Regimens	Response rate or duration	Median PFS	Median OS	Toxicity and predictive factors
ZALUTE [55]	Randomized phase III	R/M HNSCC Platinum resistant	95 191	BSC or methotrexate Zalutumumab	NA	8.4 wks* 9.9 wks*	5.2 mths 6.7 mths	Grade ≥ 3 rash more frequent with zalutumumab
De Souza [56]	Single-arm phase II	R/M HNSCC Platinum failure	45	Lapatinib	ORR: 0%	52 days	288 days for pts with no prior anti-EGFR treatment 155 days for pts. previously treated with anti-EGFR	
LUX-H&N 1 [58, 59]	Randomized phase III	R/M HNSCC Platinum failure	161,322	Methotrexate Afatinib	ORR: 5.6% ORR: 10.2%	1.7 mths* 2.6 mths	6 mths 6.8 mths	Better PFS in p16-, High PTEN expression,EGFR amplified, and low HER3 expression
Checkmate 141 [60]	Randomized Phase III	R/M HNSCC Platinum failure	236 111	Nivolumab Methotrexate, docetaxel, cetuximab	ORR: 13.3% ORR: 5.8%	2.0 mths 2.3 mths	7.5 mths; 1y OS rate 36% 5.1 mths; 1y OS rate 16.6%	Better toxicity profile with nivolumab
Keynote 040 [61]	Randomized phase III	R/M HNSCC Platinum failure	247 248	Pembrolizumab Methotrexate, docetaxel, cetuximab	ORR: 14.6% ORR: 10.1%	2.1 mths 2.3 mths	8.4 mths; 1y OS rate 37.3% 7.1 mths; 1y OS rate 27.2%	Greater OS benefit in PD-L1 TPS > 50% (11.6 vs 7.9mths) Better toxicity profile with nivolumab

*EGFR* Epidermal Growth Factor Receptor, *R/M* recurrent and/or metastatic, *mths* months, *NA* non applicable or not available, *OS* overall survival, *PFS*, progression free survival, *LFP*, larynx function preservation, *TTP*, time to progression, *AE*, adverse events, *pts*, patients, *ORR*, overall response rate, *PR*, partial response, *SD*, stable disease, *PD*, progressive disease, *BSC*, best supportive care, *PD-L1*, programmed death ligand 1, *TPS*, tumor positive score

\*p < 0.05

[18F]-fluoroazomycin-arabino- (FAZA)) that could potentially identify sub-zones of the tumor with more hypoxia (FAZA) or tumor proliferation (FLT), helping radiation oncologists to target small areas of the tumor with higher radiation doses (“dose painting”). PD-1/PD-L1 inhibitors are also investigated in the curative setting in combination with standard therapies. Questions remain concerning treatment sequences (i.e. induction versus concomitant CRT, de-escalation in HPV-positive oropharyngeal cancer, induction followed by cetuximab –RT, ...).

All patients with R/M HNSCC will progress on currently available agents. The better understanding of the molecular biology allows identification of new targets implicated in HNSCC pathogenesis. A major challenge for the next coming years will also be to identify predictive biomarkers to tailor each treatment to the most appropriate population.

### Key Points

- Early stage HNSCC is usually treated with one single treatment modality (surgery or radiotherapy).
- Locally advanced HNSCC requires a multimodal treatment that can include surgery and/or radiation therapy and/or chemotherapy.
- When surgery is the primary treatment, neck dissection is recommended in most tumors with the exception of early tumors of the vocal cord.
- Advances in microvascularized free flaps have considerably expanded the possibilities of reconstruction following resection of advanced tumors.
- Surgery has to be considered even after failure of primary non-surgical therapies
- RT is effective both as a primary modality and as an adjuvant to surgical treatment.
- IMRT is standard of care.
- For organ-preservation strategies, concomitant chemoradiation with high-dose cisplatin is standard of care in locally advanced squamous cell carcinoma of the head and neck.
- Today, the treatment of p16-positive oropharyngeal cancer is similar to p16-negative HNSCC.
- For incurable HNSCC, cisplatin and cetuximab-based treatment is the standard of care in first-line
- Nivolumab improves overall survival of patients who progress within 6 months of platinum-based chemotherapies.

### Multiple-Choice Questions

1. The most common tumor suppressor gene mutation identified in HNSCC is:
  - (a) *p53*
  - (b) *PTEN*
  - (c) *RB*
  - (d) *TSC*

2. Adding Cetuximab to radiation therapy for HNSCC
  - (a) improves only the duration of locoregional recurrence-free survival
  - (b) improves the duration of locoregional recurrence-free survival and overall survival
  - (c) increases the radiation-induced side effects
  - (d) is based on randomized trials that compared CRT with cetuximab-RT.
3. A surrogate marker for HPV infection is
  - (a) p53 expression
  - (b) p16 expression
  - (c) E6 expression
  - (d) Rb expression
4. Oncogenic HPV proteins include
  - (a) E5 and E6
  - (b) E6 and E7
  - (c) E7 and E8
  - (d) E3 and E4
5. For the evaluation of regional lymph nodes status after chemoradiation, the best exam is
  - (a) FDG PET-CT
  - (b) MRI
  - (c) CT scan
  - (d) another exam
6. Immune checkpoint inhibitors (anti-PD1 blockers)
  - (a) are superior to chemotherapy in first-line metastatic setting
  - (b) are indicated only in patients with tumor expressing PD-L1
  - (c) induce higher tumor responses and survival in PD-L1 positive tumors even though patients with PD-L1-negative tumors could also benefit from them
  - (d) present a worse toxicity profile than chemotherapy
7. Which pathway is not directly activated by signaling through EGFR?
  - (a) MAPK pathway
  - (b) PI3K pathway
  - (c) RB pathway
  - (d) VEGF pathway
8. The anti-EGFR panitumumab
  - (a) is the only monoclonal antibody that improves survival in metastatic HNSCC
  - (b) induce ADCC reaction that explain superior efficacy compared to cetuximab

- (c) is not approved as standard treatment in metastatic HNSCC in association with platinum-based chemotherapy
  - (d) is approved as standard treatment in combination with radiotherapy
9. Induction chemotherapy in locally advanced head and neck cancer
- (a) is superior to chemoradiotherapy alone in long-term survival in locally advanced HNSCC
  - (b) is superior in improving the rates of larynx preservation compared to chemoradiotherapy alone
  - (c) is not accepted as standard of care in locally advanced HNSCC
  - (d) is a standard of care in HPV-negative locally advanced HNSCC
10. An oncogenic HPV virus is
- (a) HPV type 6
  - (b) HPV type 11
  - (c) HPV type 16
  - (d) HPV type 13
11. Regarding concomitant chemoradiation
- (a) Should be given only as adjuvant treatment
  - (b) is a standard of care for locally advanced disease with cisplatin
  - (c) IMRT is under investigation
  - (d) is inferior to induction therapy
12. Regarding HPV-positive HNSCC,
- (a) has a worse prognosis compared with HPV-negative HNSCC
  - (b) the role of HPV infection is controversial outside the oropharynx
  - (c) p16 positive oropharyngeal cancer should be treated with a less intense treatment compared to p16-negative oropharyngeal cancer
  - (d) the gold standard to detect HPV infection is HPV serology.
13. Regarding salvage surgery after chemoradiation,
- (a) should never be used
  - (b) is an adequate treatment possibility for selected patient
  - (c) should be given in combination with chemotherapy
  - (d) should be given in combination with radiation therapy
14. The more frequent histology for head and neck cancer is
- (a) squamous cell carcinoma
  - (b) sarcoma
  - (c) adenocarcinoma
  - (d) mucoepidermoid histology

15. The most frequent genetic alteration in HPV-positive HNSCC is
- (a) p53
  - (b) CDKN2A
  - (c) CCND1
  - (d) PI3KCA
16. Regarding the initial work-up for HNSCC, which statement is incorrect
- (a) Flexible fiberoptic endoscopy allows assessment of the tumor size and extension to adjacent structures, such as vocal cord
  - (b) Around 10% of the patients will have distant metastasis
  - (c) A rigid endoscopy under general anesthesia is not very useful is the flexible fiberoptic examination has been performed.
  - (d) All upper aerodigestive tract must be meticulously assessed in order to exclude other synchronous primaries.

**Multiple Choices (the Correct Answer Is in Bold)**

1. **The most common tumor suppressor gene mutation identified in HNSCC is:**
- (a) *p53*
  - (b) *PTEN*
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- (a) E5 and E6
  - (b) **E6 and E7**
  - (c) E7 and E8
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5. **For the evaluation of regional lymph nodes status after chemoradiation, the best exam is**
- (a) **FDG PET-CT**
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6. **Immune checkpoint inhibitors (anti-PD1 blockers)**
- (a) are superior to chemotherapy in first-line metastatic setting
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  - (b) is superior in improving the rates of larynx preservation compared to chemoradiotherapy alone
  - (c) **is not accepted as standard of care in locally advanced HNSCC**
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- (a) HPV type 6
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**11. Regarding concomitant chemoradiation**

- (a) Should be given only as adjuvant treatment
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**12. Regarding HPV-positive HNSCC,**

- (a) has a worse prognosis compared with HPV-negative HNSCC
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- (c) p16 positive oropharyngeal cancer should be treated with a less intense treatment compared to p16-negative oropharyngeal cancer
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**13. Regarding salvage surgery after chemoradiation,**

- (a) should never be used
- (b) **is an adequate treatment possibility for selected patient**
- (c) should be given in combination with chemotherapy
- (d) should be given in combination with radiation therapy

**14. The more frequent histology for head and neck cancer is**

- (a) **squamous cell carcinoma**
- (b) sarcoma
- (c) adenocarcinoma
- (d) mucoepidermoid histology

**15. The most frequent genetic alteration in HPV-positive HNSCC is**

- (a) p53
- (b) CDKN2A
- (c) CCND1
- (d) **PI3KCA**

**16. Regarding the initial work-up for HNSCC, which statement is incorrect**

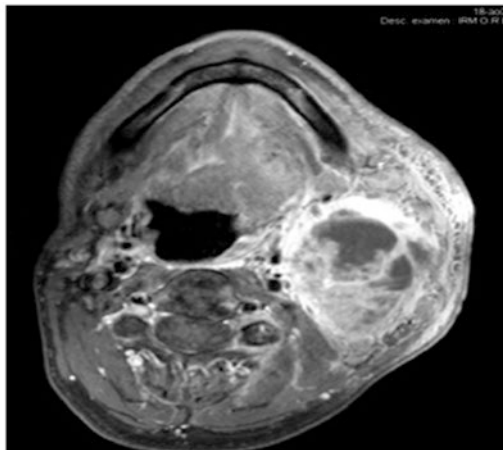
- (a) Flexible fiberoptic endoscopy allows assessment of the tumor size and extension to adjacent structures, such as vocal cord
- (b) Around 10% of the patients will have distant metastasis
- (c) **A rigid endoscopy under general anesthesia is not very useful if the flexible fiberoptic examination has been performed.**
- (d) All upper aerodigestive tract must be meticulously assessed in order to exclude other synchronous primaries.

**Clinical Case**

A 52 years old patient was admitted to the head and neck surgery department for a large cervical mass. The patient has never smoked and drinks one beer per day. The cervical CT-scan revealed a 7 cm cystic left mass localized in level II-III (Fig. 31.5). Clinical examination showed no evident primary. Therefore, FNA was performed



**Fig. 31.5** Cervical CT-scan showing a 7 cm cystic left mass localized in level II-III, that was confirmed as a squamous cell carcinoma on fine needle aspiration



and concluded in the presence of a squamous cell carcinoma. FDG-PET scan confirmed high metabolic activity inside the neck mass and pointed out a potential primary tumor inside the left tonsil, no distant metastatic disease was identified. Endoscopy was then performed under general anesthesia and showed focal induration inside the left tonsil. A biopsy confirmed the diagnosis of undifferentiated squamous cell carcinoma and strong p16 staining in more than 75% of the tumor cells. According to AJCC 8th tumor staging edition, this HPV-positive oropharynx tumor was classified cT1cN3 (stage III). Treatment consisted in conventional IMRT (70 Gy) with concomitant high-dose cisplatin (100 mg/m<sup>2</sup> delivered on day 1, 22, and 43 of radiation therapy).

Twelve weeks after the end of chemoradiation, a new FDG-PET demonstrated no metabolic residual activity in the neck despite persistence of a 1.6 cm large node on CT-scan. As patient had an HPV positive disease and negative FDG PET activity, neck dissection was not performed and patient was regularly followed in the head and neck surgery department. No recurrence occurred during the 2 years follow-up.

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# Chapter 32

## Thyroid Cancer



**Washington Luiz de Oliveira Gois Filho, Janssen Loiola Melo Vasconcelos, José William Ferreira Junior, Eric Fernandes Souza, Ricardo Lincoln Pinto Gondim, Erick Siqueira Campos de Oliveira, and Ramon Andrade De Mello**

**Abstract** The incidence of thyroid cancer has increased significantly in recent decades in several parts of the world. The routine request of ultrasonography has contributed to the increase of the cases, being each time more and more common the diagnoses in asymptomatic ones. Thyroid cancer is the fifth most common cancer in women in the United States, and the largest cause of endocrine neoplasia in the world.

**Keywords** Thyroid cancer · Target therapy · Chemotherapy

### 32.1 Introduction

The incidence of thyroid cancer has increased significantly in recent decades in several parts of the world. The routine request of ultrasonography has contributed to the increase of the cases, being each time more and more common the diagnoses in asymptomatic ones. Thyroid cancer is the fifth most common cancer in women in the United States, and the largest cause of endocrine neoplasia in the world. It represents around 0.5% of malignant neoplasms in men, and 1.5% in women. The statistics show that more than 62,000 new cases occurred in men and women by 2015 in the United States. Although the incidence is steadily increasing, mortality from thyroid cancer has changed minimally over the past five decades. The challenge faced by doctors treating thyroid neoplasms is to balance the therapeutic

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approach so that patients with lower-risk disease or benign thyroid nodules are not over-treated. At the same time, doctors need to recognize which patients with more advanced or high-risk disease need a more aggressive treatment approach. Thyroid neoplasms present a wide range of clinical manifestations of indolent tumors with low mortality in most cases, and very aggressive malignancies – for example, anaplastic thyroid neoplasia [1–6].

## 32.2 Clinical Presentation and Epidemiology

Usually, the symptomatology of malignant thyroid diseases is the presence of a nodule, usually hardened, in the thyroid store, painful or not, of slow growth. As an initial symptom, there may be metastatic lymph node enlargement. As the malignant nodule does not affect the function of the gland, there are no systemic symptoms, unless, for example, the cancer is followed by previous thyroiditis with hypothyroidism. In more advanced cases, one may have a hardened, painful anterior cervical mass with respiratory symptoms such as dysphonia or respiratory stridor. However, in many cases, the patients are asymptomatic, and the diagnosis is made through routine exams.

Thyroid nodules are being identified more frequently in clinical practice, due to the use of imaging diagnosis. Palpable nodules can be found in 5.3–6.4% of women, and in 0.8–1.6% of adult men, a prevalence that may increase if the investigation is performed by ultrasonography (USG), which is capable of detecting nodules in 20–70% of the adult population. The clinical importance of presenting a thyroid nodule is based on the need to rule out thyroid cancer. About 5–15% of nodules are malignant, depending on age, sex, radiation exposure, and family history.

In recent studies using new high-resolution imaging techniques, thyroid nodules, which would never have been diagnosed in the past, are being identified. Although more than 90% of the lesions are small and not palpable, or benign lesions that will never become clinically significant, some lesions are palpable or malignant. The identification of malignant thyroid nodules is important, especially those that will cause morbidity if not diagnosed early. To distinguish patients belonging to the low-risk and high-risk groups, complete history and physical examination, laboratory tests, neck USG are required; and for properly selected patients, fine needle aspiration (FNA). Autonomic thyroid nodules that trigger hyperthyroidism should be identified prior to biopsy in order to avoid complications and ensure imaging and appropriate treatment. Radionuclide thyroid scintigraphy should be performed only in patients with suppressed thyroid stimulating hormone (TSH). If TSH is suppressed, free thyroxine (T4L) or triiodothyronine (T3) dosing should be performed to confirm thyrotoxicosis. Approximately 10% of the palpable nodules present sufficient autonomy to reduce TSH levels, which is a finding suggestive of benignity. If TSH concentrations are elevated, the anti-thyroperoxidase (anti-TPO) titles should be checked to confirm the diagnosis of Hashimoto's thyroiditis.

The USG of thyroid, especially if using the latest generation of devices, allows a detailed anatomical study of the nodules, and identification of characteristics that

may be associated with an increased risk of malignancy. The presence of microcalcifications, irregular borders and hypoechogenicity are findings suggestive of malignancy; however, the specificity of these characteristics is relatively low – 65 to 68%. The addition of Doppler increases the diagnostic accuracy: absence of vascularization or exclusively peripheral vascularization are data suggestive of benignity, whereas predominant or exclusively central vascularization suggests malignant disease. USG can also help perform fine-needle aspiration (FNA), facilitating the collection of material and reducing the need for new punctures by inadequate collection of material.

### 32.3 Classification and Characteristics of Thyroid Neoplasms

The distinct thyroid cancer is the most common form of the thyroid neoplasm, responsible for over 95% of cases, and originates from the thyroid follicular epithelial cells. Papillary thyroid carcinoma has, in general, indolent, low aggressiveness, producing regional lymph node metastases. It may produce metastases at distance, but they are less common. At the older ages, mature women over 50 years and men over 40–45 years, it can be more aggressive.

Follicular carcinoma produces hematogenous metastases, firstly to the lungs and bones most of the time, and usually affects higher age people comparing with the carrier of a papillary carcinoma. It produces metastases at a distance 5–20% of follicular cancers. There are two types of thyroid follicular cancers: minimally invasive follicular cancer, in which the prognosis reaches up to 100% cure, and the follicular cancer invasive, with 25–45% cure.

In follicular neoplasms, in follicular adenoma, there may be thin or partially encapsulated capsule, while in follicular carcinoma there is often neoplastic invasion through the capsule.

The follicular cancer of Hürthle cells comes from the follicular cancer that, in general, is more aggressive, responsible for about 3–5% of all types of thyroid cancer.

Exposure to electromagnetic radiation, especially during early childhood, is a high risk factor for papillary carcinoma, and its genetic mechanisms of origin have been studied. The abnormality found in up to 25% of these tumors is the translocation RET/papillary thyroid carcinoma (PTC), on which have been described about 10 types – the main ones are RET/PTC-1 (most common in adults) and RET/PTC-3 (most common in children exposed to radiation). Another abnormality considered is the activating mutation of BRAF, detectable in 35% of papillary carcinomas and associated with poor prognosis and progression to anaplastic tumor. The mutation activator proto-oncogene RAS was evidenced in 18% of papillary tumors, but also in anaplastic (58%) and follicular (32%) lesions.

Follicular tumors, whether benign or malignant, exhibit RAS- activating mutations in 1/3 of the cases. A more specific mutation of follicular carcinoma is the

paired box gene 8 translocation (PAX-8)/peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ), detectable in more than 50% of these lesions, but also in adenomas.

Anaplastic thyroid cancer is a rare form of thyroid cancer (< 1%), which usually presents itself as an increase in rapid growth of the neck diameter, occurring in general in patients over 60 years. Patients often develop hoarseness, dysphagia, and dyspnea. In the examination, most patients with anaplastic thyroid cancer have a large, firm palpable mass in the thyroid with or without cervical adenopathy. This finding should lead to rapid assessment and mass biopsy. A survey of metastases often reveals loco-regional disease and distant metastases. The most common place of distant metastatic disease is the lung, followed by bones and brain. Anaplastic thyroid neoplasm often arises and may coexist with differentiated thyroid cancer, but it may also occur again. Doctors should suspect any anaplastic transformation in patients with a history of long-term thyroid differentiation if the above symptoms are shown. In this case, a referral to a center with experience in treating cancer and thyroid anaplastic is recommended, since they are rare tumors that have a poor prognosis cause of rapid tumor growth.

An anaplastic carcinoma marker is the loss of the p53 tumor suppressor gene, which can be demonstrated even in differentiated thyroid tumors, in which it predicts the evolution to non-differentiation.

Medullary thyroid cancer is uncommon, responsible for 1–2% of all thyroid cancers. In contrast with differentiated thyroid cancer, medullary thyroid carcinoma originates in the parafollicular neuroendocrine cells of the thyroid, and most commonly presents as a solitary thyroid nodule in patients between the fourth and sixth decade of life. Occasionally, cervical lymphadenopathy is the first manifestation because the disease often metastasizes to cervical lymph nodes – 70% of patients with palpable medullary thyroid carcinoma have evidence of cervical metastases in surgery.

Some patients show a classic case of a thyroid nodule, flushing and diarrhea, clinical presentation suggestive of diffuse metastatic disease. A quarter of the cases of medullary thyroid carcinoma occur in patients with multiple endocrine neoplasia syndrome hereditary variability whose expression determines three distinct syndromes: multiple endocrine neoplasia 2A (MEN 2A) associated with hyperparathyroidism, and pheochromocytoma associated with MEN 2B pheochromocytoma and mucosal neuromas, medullary carcinoma of the thyroid hereditary. There is an association medullary carcinoma of thyroid which involves RET proto-oncogenes.

## 32.4 Genetic Changes Associated with Thyroid Cancer

Findings from DNA sequencing studies of thyroid cancer revealed the genetics for large parity of thyroid neoplasms. Most thyroid carcinomas have mutations along cellular signaling pathway of MAP kinase (Mitogen Activated Protein Kinases). This pathway transmits growth signals from the plasma membrane to the nucleus, and plays a central role in the regulation of cell proliferation of the differentiated cancer of the thyroid and anaplastic thyroid carcinoma.



The most frequent mutation in non – medullary thyroid cancer is the BRAFT1799A mutation, which occurs exclusively in papillary thyroid cancer and anaplastic thyroid cancer. Mutations in the RAS family of oncogenes also occur frequently in RAS mutations of cancer. The thyroid neoplasia occurs more frequently in carcinoma follicular thyroid and follicular variant papillary thyroid cancer. Chromosomal translocations also occur in thyroid carcinomas. These genomic rearrangements lead to the expression of new fusion oncogenes, which initiate events in many thyroid neoplasms. In 7% of all thyroid papilliferous carcinoma occur mutation of RET oncogene. Thyroid carcinoma has less common translocation, partners include BRAF, the **neurotrophic tyrosine kinase receptor (NTRK)**, anaplastic lymphoma kinase (ALK) and thyroid adenoma associated (THADA).

Mutations in the RET proto-oncogene are the cause of most cases of medullary thyroid carcinoma, while a small proportion is due to RAS point mutations. Mutations in the RET can predispose patients to early development of medullary thyroid carcinoma as a component of the type of multiple endocrine neoplasia syndromes 2A and 2B. In such cases, younger patients are likely to have hereditary disease. There are strong genotype-phenotype associations with specific RET mutations, that predict both the age of onset, and clinical aggressiveness of medullary thyroid carcinoma. Prophylactic thyroidectomy is often indicated, but specific recommendations are based on the patient ‘s age and inherited mutation. Since 1–7% of patients with apparently sporadic spinal cord carcinomas carry germline mutations in RET, the evaluation of hereditary RET germnative mutation should be recommended for all patients with medullary thyroid carcinoma regardless of their family history or age.

### 32.5 Evaluation of Thyroid Nodules

Semi logical data may help considerably in assessing the risk of a thyroid nodule (Table 32.1). However, these findings of high diagnostic value have low sensitivity, since most thyroid carcinomas are asymptomatic nodules.

**Table 32.1** Degree of suspection

High degree of suspicion	Family history of familial spinal cord carcinoma
	Family history of multiple endocrine neoplasia
	Hardened nodule attached to adjacent tissues
	Fast growth
	Paralysis of vocal folds
Moderate degree of suspicion	Cervical adenomegaly
	Male
	Age <20 years or older >70 years
	Previous history of cervical irradiation
	Nodule >4 cm or with central liquefaction

TSH is indicated in patients with thyroid nodules. The suppressed TSH should be supplemented with free T3 and T4 dosages to confirm thyrotoxicosis.

Approximately 10% of palpable nodules have sufficient autonomy to reduce the levels of TSH, which is a strongly suggestive finding of benignity. Thus, for autonomous nodules demonstrated in the thyroid mapping ("hot" nodules), there is no need for FNAB (**Fine needle aspiration biopsy**).

If TSH concentrations are high, antithyropoxidase titles (anti-TPO) must be tested to confirm the diagnosis of Hashimoto's thyroiditis. The risk of thyroid lymphoma is 67 times greater in patients with Hashimoto's thyroiditis, but nonetheless, lymphoma is an uncommon diagnosis.

The dosage of calcitonin in all thyroid nodules is controversial. In fact, early diagnosis and appropriate treatment (total thyroidectomy with cervical emptying) reduce substantially the risk of recurrence and dissemination, and the serum calcitonin dosage has superior sensitivity to conventional cytological examination in identifying spinal of thyroid. However, the rarity of this etiology (1 in 250 nodules), low sensitivity of most commercial available calcitonin assays and the high cost of research make population screening impractical.

For risky patients (relatives of patients with endocrine neoplasia Multiple or type 2 familiar medullary carcinoma), baseline calcitonin dosage and calcium or pentagastrin infusion test are warranted to confirm the diagnosis.

Calcium infusion test is based on the fact that the C cells release calcitonin when serum calcium increases. In this test, calcitonin is given before and after (2, 5 and 10 min) of the injection of 2 mg of ion calcium per kg of patient weight. The increase of calcitonin to values above 100 pg/ml suggest medullary thyroid carcinoma.

The pentagastrin test is done with the IV injection of 0.5 µg/kg of body weight and collection of calcitonin at times 0, 2, 5 and 10 min. Elevation of calcitonin above 100 pg/ml suggests CMT.

The last generation of Thyroid ultrasound with high frequency transducers (greater than 10 MHz) allows detailed anatomical study of the nodules and identification of characteristics that seem to be associated with an increased risk of malignancy. Presence of micro-calcifications, irregular borders and hypoechogenicity are ultrasonographic findings suggestive of malignant neoplasm. However, the specificity of these characteristics is relatively low (66%).

The addition of Doppler increased accuracy diagnosis: absence of vascularization or exclusively peripheral vascularization are suggestive of benignity, whereas predominant or exclusively central vascularization suggests malignant disease.

Another use of ultrasonography is the orientation for FNAB, facilitating the collection of material and reducing the need for new punctures by inadequate collection of material.

Currently, FNAB is considered the most reliable and accurate examination in the diagnosis of thyroid nodular disease. This is a safe, low-invasive, low-cost and easy-to-achievement. The use of this method on a large scale reduced the number of thyroidectomies by 50%, time that doubled the prevalence of cancer in the cases operated. There are no contraindications to FNAB (including use of antiplatelet agents) platelets and anticoagulants), and there is no risk of dissemination neoplas-

tic by the puncture path. The main side effect is local discomfort, which lasts less than 24 h and can be relieved with cold compresses or simple analgesics.

FNAB should be performed on any nodule larger than 1 cm in diameter or with ultrasonography suggestive of malignancy or clinical history of risk, except when there is suspicion of nodule through the thyroid mapping.

The system of Bethesda used to report thyroid cytopathology include six categories. The diagnostic category includes benign nodules 9 (category 2), which can be administered safely with periodic neck USG; nodules that are malignant (category 6) or probably malignant (category 5) usually need surgery. If cytology results are not diagnostic (category 1), the nodule should be re-aspirated. Undetermined outcomes (categories 3 and 4, the latter most likely to be malignant) may be managed surgically or with close clinical monitoring, depending on clinical risk factors, USG standards, and patient preferences.

For patients in diagnostic categories 3 and 4, where in the diagnosis or thyroid cancer deletion is unclear, it may be used approaches of molecular biology techniques, using gene mutation profiles and gene expression. A positive test for a mutation in genotyping panels has a high predictive value for thyroid cancer. In contrast, expression of the classifier gene offers a strong negative predictive value, but a suspected result is predictive of thyroid cancer in only 50% of cases.

The immunocytochemistry can increase the specificity of cytology. Calcitonin is specific to medullary thyroid carcinoma, which is derived from parafollicular cells (C Cells). Other markers such as galectin-3 and cyclooxygenase-2 are more expressed in malignant thyroid neoplasms benign, but the sensitivity of these techniques is not large enough to justify their routine use.

Despite the mapping of thyroid with traditional isotopes such as  $^{131}\text{I}$ ,  $^{123}\text{I}$  and  $^{99\text{m}}\text{Tc}$  to be useful for functional evaluation of goiters toxic looking for areas hyper capturing, the finding of an area hypo capturing (“Cold”) has low specificity for malignant thyroid neoplasms, since 90% of thyroid nodules have this pattern of capture and represent only 5% carcinomas.

Recent studies with other radioisotopes ( $^{99\text{m}}\text{Tc}$ -methoxy -iso-butyl – lisonitrile,  $^{201}\text{Tl}$  and  $^{18}\text{F}$ -deoxy – glucose) have shown promising results in differential diagnosis of thyroid nodules.

TSH	Perform in all patients with thyroid nodule Suppressed TSH suggests benignity
Calcitonin	High sensitivity for medullary thyroid carcinoma
USG	Findings suggestive of malignancy Hypoechoogenicity Micro-calcifications Irregular edges
FNAB	Indicated in any nodule greater than 1 cm or with characteristics of malignancy
Nuclear medicine	Functional evaluation of toxic goiters

## 32.6 Treatment of Differentiated Thyroid Cancer

Cervical USG plays a key role in the assessment to decide the appropriate treatment, providing surgeons with fundamental information on size, location, number of tumors and lymph nodes, and on local invasion of surrounding tissues. In up to a third of patients with differentiated thyroid cancer, nodules injuries are identified on preoperative examination, and, in two thirds of these cases, the results lead to a surgical plan revision.

Primary treatment decisions are based on preoperative risks, which includes clinical, imaging, and cytological data. The choices depend on the location or locations and the extent of the disease; there is also a risk of unidentifiable outbreaks of the disease (prophylactic surgery). The recent ATA guidelines are more conservative, considering the favorable evolution showed by studies about these patients. Lobectomy is an option for unifocal tumors smaller than 4 cm, with no evidence of extra-thyroidal extension or lymph node metastasis. The results of several large studies have shown that unilateral and bilateral resections are associated with similar long-term survival. In these cases, overall survival is also not affected by the presence of lymph node metastases. With an intact lobe, many patients can avoid thyroid hormone replacement therapy throughout life. The complications rates associated with lobectomy are about half of those reported with total thyroidectomy in the presence of small, non-invasive tumors. In the lobectomy, the central compartment should be inspected, and if nodal disease is detected, the procedure should be reverted to total thyroidectomy with compartmental cervical dissection. Rare recurrences that develop long-term when following the patients treated with lobectomy can be detected easily, and appropriately controlled with surgery, without changes of survival. That evidence is based on the results of case-control studies and data records. The no-surgery handling may be an option for carefully selected patients who show papillary micro-carcinomas ( $= 1$  cm) with no evidence of metastasis in the cervical lymph nodes. Researchers in Japan have found strong evidence of safety and effectiveness of active surveillance in these surgical cases. Clinical surveillance is the standard course in this country for thyroid micro-carcinoma. Such conduct is not recommended in other countries.

After surgery, a next decision comes regarding the need for ablation with radioactive iodine, or TSH suppression, or both. This evaluation is performed conventionally based on the tumor-lymph node-metastasis (TNM) system. This system was designed to predict mortality, and is less effective in estimating the likelihood of disease recurrence, which is more relevant to planning follow-up. In 2009, ATA goes on to consider the need to estimate the recurrence risk, proposing a new system which identifies high, medium and low risk for recurrence.

The decision to administer radioactive iodine treatment after total thyroidectomy is often justified by the need to eliminate residual thyroid tissue. The ability of this tissue to incorporate iodine and produce thyroglobulin complicates efforts to identify thyroid tissue persistent or recurrent neoplastic scintigraphy with iodine 131 and assays of serum thyroglobulin. This logic is now being challenged. In the last

two decades, the use of full-body scintigraphy (PCI) or PCI with iodine 131 has declined sharply, being replaced for diagnostic methods comparatively less used than cervical USG, because it is more sensitive and has a cost-advantageous, and it does not expose the patient to radiation, besides the lack of adverse effects.

The combined cervical USG with serum thyroglobulin assays are the most sensitive methods to detect persistent disease and to tailor subsequent diagnostic strategies and therapies.

The use of radioiodine is also advocated as adjuvant treatment, with the objective of improve long-term results by shedding hidden microscopic focus of neoplastic cells into the remaining thyroid tissue or into other parts of the body. This practice has also been questioned in the last decade: the guidelines, which now recommend the selective use of radioactive iodine, based on individual risk use the lowest dose of radiative iodine needed to ensure treatment success.

Finally, radioactive iodine can be used to identify patients with distant metastatic – because it is sensitive to radioactive iodine – and also serves as a treatment of distant disease. Unfortunately, many patients are refractory to radioactive iodine; thus, for such patients, this strategy would not be effective in detecting or treating distant disease.

Circulating TSH stimulates the proliferation of normal thyrocytes and most thyroid cancer cells. For this reason, TSH-suppressive doses of thyroid hormone therapy have traditionally been used after surgery. This approach significantly reduces the recurrence and cancer – related mortality in patients with differentiated thyroid cancer. However, the amount of suppression needed to achieve these goals is not clear. In high risk patients, reduce concentrations of TSH to less than 0.1 mU/L can improve clinical outcomes, but moderate reductions (for normal subnormal TSH) can also improve outcomes. However, hyperthyroidism subclinical changes induced by TSH may negatively affect bone (causing postmenopausal osteoporosis) and heart (causing angina in patients with coronary heart disease, and fibrillation at trial in elderly patients). The probability of complications should be assessed compared with the risk of increasing tumor cell proliferation, based on the individual's risk assessments for persistent or recurrent disease.

After 6–12 months of surgery, the patient's risk should be reviewed based on his response to primary treatment. The reassessment of these patients involves the measurement of thyroglobulin, cervical USG, and other tests as needed. The results are essential for planning the next year follow-up, considered important since 7% of recurrences are discovered during the first 5 years after surgery. Even so, the risk estimated is continuously updated and reviewed during follow-up. With this approach, a substantial proportion of patients with differentiated thyroid cancer, including some whose initial staging revealed a high risk of persistent or recurrent disease, may at some point be reclassified as having a lower risk of recurrence, and lower intensity. Recurrences detected during the surveillance period are usually managed with observation (for clinically insignificant or very small lesions) or with comprehensive compartmental surgery.

### **32.7 Radioiodine Therapy Is Recommended for Patients with High Risk Disease**

These conditions indicate the latter risk:

- Macroscopic tumor invasion;
- Resection incomplete tumor with evident residual disease;
- Metastases at a distance;
- thyroglobulin levels increased suggesting metastatic disease;
- N1 disease in the staging with lymph node >3 cm in its largest diameter;
- Follicular carcinoma with significant vascular extension.

In patients with intermediate risk factors – including microscopic soft tissue invasion, presence of cervical lymph node disease, histologically aggressive and multifocal tumor, radioactive iodine therapy may be considered. Ten years before this therapy was standard treatment for all patients with thyroid carcinoma.

In relation to suppressive therapy with thyroid hormone, it is recommended that patients with high-risk disease should maintain TSH levels below 0.1 m/UL. For those with an intermediate risk between 0.1–0.5 m/UL, and for low-risk patients the low normal values. Annually, recurrence of the disease can be investigated in patients with suppressive therapy with levothyroxine suspension up to TSH >30 m/UL, or with recombinant human TSH, performing PCI and thyroglobulin dosage. In other patient returns, cervical USG and non-stimulating thyroglobulin dosage are recommended.

### **32.8 Anaplastic Thyroid Carcinoma**

The anaplastic thyroid carcinoma can present several histomorphological abnormalities, leading to confusion in the definition of the organ of disease origin. This confusion can lead to a delay in diagnosis and early treatment plan. Once diagnosed, patients should be evaluated quickly, and their airways verified by fiber optic laryngoscope. Specialized centers should evaluate the possibility of resection of the disease. Patients with primary tumors not removed, without detectable distant metastases are generally referred to palliative chemoradiation. If the locoregional disease is an imminent threat, radiation chemotherapy should be given first. For those patients whose airways are not at risk or is already stabilized by tracheotomy, systemic chemotherapy with cytotoxic drugs, or preferably enrollment in a clinical trial should be considered.

## 32.9 Treatment of Medullary Carcinoma of Thyroid

The only effective treatment for medullary carcinoma is surgery, and its success depends on the clinical stage of the patient and the adequacy of the initial therapeutic approach. Current, there are no comparable therapies yet, such that resections should encompass all neoplasia with tumor-free margins. However, some patients with clinically apparent lymph node metastases at the time of diagnosis may reach undetectable tumor markers. As with differentiated thyroid cancer, imaging diagnosis before surgery is crucial to indicate the appropriate surgical intervention. All patients with preoperative diagnosis of medullary thyroid cancer should be subjected to ultrasound neck and measurement of tumor markers (antigen calcitonin and carcinoembryonic). Also, determine if the patient has an inherited or sporadic disease is crucial because patients with multiple endocrine neoplasia type 2 may have pheochromocytoma or hyperparathyroidism primary, or both; and in this case it is important to solve the pheochromocytoma before surgery for medullary carcinoma. If the patient has primary hyperparathyroidism, thyroid surgery should be adapted to include parathyroidectomy. The lymphadenectomy of the central compartment and bilateral cervical chains should be routinely performed.

Radiotherapy and chemotherapy are not effective in the treatment of medullary carcinoma, but may be indicated as palliative. Authors have linked the application of external radiotherapy to evidence of improved control of locoregional disease in patients with advanced tumors, although they have not been made associations with overall survival increase.

The referral to genetic counseling for patients with hereditary medullary carcinoma of the thyroid is recommended.

### 32.10 Tumor Markers on Preoperative Stage

If the concentration of calcitonin in the preoperative period is greater than 146 pmol/L, a research of distant metastatic disease must be performed. The image recommended for this case includes cervical and chest computed tomography (CT) and magnetic resonance imaging (MRI) of the liver with contrast. Bone metastases are preferably evaluated by NMR of axial skeleton. In the absence of substantial distant metastatic disease, the preferred surgery is total thyroidectomy with bilateral central cervical dissection. The side dissection of the neck and suspected cervical ultrasound is confirmed by cytology aspiration. The ATA guidelines for the treatment of medullary thyroid cancer recommend contralateral cervical dissection in patients with cervical disease based on calcitonin concentrations greater than 58 pmol/L; however, this recommendation remains controversial.

The long –term handling of medullary thyroid carcinoma consists of observation. Patients need hormone thyroid replacement, but there is no indication of therapy suppressing TSH, same way it is with differentiated cancer high-risk thyroid. Tumor markers must be checked 3 months after the surgery (calcitonin of carcinoembryonic antigen) to determine if the patient has persistent disease. External beam radiation should be used with moderation as it can limit the surgical intervention in the future due to induction of fibrosis.

Patients with undetectable tumor markers and normal image after surgery should continue to be followed every year, and those with tumor markers persistent should be monitored more closely to progression. The two times increase in calcitonin and the antigen carcinoembryonic is a useful measure, because they are predictive of results and tumor aggressive behavior. Patients with calcitonin and increased carcinoembryonic antigen within 6 months have shorter overall survival.

### **32.11 Systemic Treatment of Thyroid Carcinoma**

Systemic treatment is considered for patients who are refractory to therapy with radioactive iodine. The default setting of these patients includes metastatic lesions that have no uptake in the PCI, or one or more lesions which have no absorption in the PCI or progression of injuries that are captured by PCI. Most definitions also include patients who received more than 600 mCi cumulative dose of radioactive iodine, because these patients do not seem to benefit from further treatment.

Localized treatments may be applied for patients with progressive disease, thereby delaying the need for systemic treatment. For example, external beam radiation or embolization for bone or liver metastases may be considered. In patients with locoregional disease, surgery should be considered in the proper configuration, and metastasectomy can be used for low significant metastatic disease in order to diminish morbidity.

In recent years, the United States, the Food and Drug Administration (FDA) and the European Medicines Agency approved two kinase inhibitors for use in differentiated thyroid cancer: Sorafenib and lenvatinib, drugs with properties antiangiogenic. Other classes of drugs have been studied for differentiated thyroid cancer.

For medullary thyroid carcinoma, both the vandetanib and cabozantinib are approved for treatment in the United States and the European Union. Many patients with metastatic carcinoma or recurrent differentiated thyroid cancer and thyroid medullary carcinoma have indolent disease. Thus, these drugs are reserved for patients with progressive disease or for those with disease that is threatening vital structures or causing substantial clinical symptoms. The patients with differentiated thyroid carcinoma disease should be treated with radioactive iodine before being considered systemic treatments.

So far, none of the trials showed a benefit of overall survival when comparing drugs with placebo.



### Clinical Case 1

A previously healthy 36-year-old female patient reports having noticed an increase in cervical volume anterior to the right about 8 months ago. She states she does not feel pain, there is no skin temperature or coloration changes, nor dysphagia or dyspnea. Regarding the physical examination, a nodule of about 2 cm is felt, in a hardened, painless consistency, fixed to deep structures, in the middle third of the left lobe of the thyroid. A cervical ultrasound is performed to certify the presence of this nodule. Thyroid function tests are normal.

### Clinical Case Reviewed

In the above case the patient presents a nodule with more than 1 cm indicating FNA. The presence of normal thyroid function also reinforces this behavior.

The cytological examination of FNAB of the patient's nodule revealing psammomatous bodies and cleaved core with the appearance of "Annie orphan" are findings compatible with a papillary carcinoma. In this case, the patient should undergo thyroidectomy and radioiodine therapy, and follow-up should be performed with serum thyroglobulin dosage, cervical ultrasound, and whole body radioiodine monitoring.

### Clinical Case 2

A 58-year-old patient has a nodule in the thyroid gland measuring 2.5 cm of diameter in the right lobe, with no palpable cervical adenopathy.

### List 3 Exams Indicated for Diagnosis

The patient presented a 2.5 cm uni-nodular goiter without adenopathy. The diagnosis of thyroid neoplasm has to be removed. For best evaluation, Doppler ultrasonography can be done (nodule vascularization pattern may aid in evaluation). The second important exam is fine needle aspiration for nodule pathologic assessment. The x-ray of aerial column is also important for evaluation of tracheal deviation, a possible surgical indication.

### With Cytology Showing Cells with "Frosted Glass" Cytoplasm and Nuclear Crevices, What Are the Diagnosis and Treatment?

Cytology is characteristic of papillary thyroid carcinoma, a very differentiated thyroid tumor. Treatment is based on total thyroidectomy and cervical chain exploration. In lymph node metastasis cases, cervical emptying is indicated.

### Questions

1. Check the alternative that in the evaluation of a thyroid nodule by USG show three suggestive signs of a benign lesion (B) and three of malignant (M):
  - (a) (B) regular limits, irregular halo, micro calcifications  
(M) cystic areas, gross calcifications, hyper vascularization.
  - (b) (B) present Halo, hypo echogenic, "eggshell" calcifications.  
(M) hyperechoic, peripheral vascularization and micro calcification.
  - (c) (B) Hyperechoic, micro calcifications, peripheral vascularization  
(M) irregular or absent halo, hypo echogenic, solid.
  - (d) (B) absent halo, hyper echogenic, cystic.  
(M) hyper vascularization, micro calcifications, hypo echogenic.

- (e) **(B) Hyperechoic, “eggshell” calcifications, vascularization peripheral (M) hypo echogenic, micro calcifications, hyper vascularization.**
2. Regarding the **thyroid nodules**, considering the statement below, we can say:
- I. The solid ultrasound nodules, in the upper polo, present higher risk of malignancy.
  - II. Ultrasound-guided puncture represents the main diagnosis examination.
  - III. Doppler has no role in the evaluation of these nodules.
  - IV. Ultrasound-guided puncture has no advantages when compared to conventional puncture.
  - V. In the follicular lesion puncture, it represents a suspicious diagnosis, being difficult to differentiate follicular adenoma from follicular carcinoma.
- (a) The statements (I), (II) and (III) are correct.
  - (b) The statements (II), (IV) and (V) are wrong.
  - (c) **The statements (I), (II) and (V) are correct.**
  - (d) The statements (I), (III) and (IV) are wrong.
  - (e) The statements (I), (III) and (V) are correct.
3. Regarding the malignant neoplasms of the thyroid gland, we can affirm that:
- (a) Papillary carcinoma in children, in most of the cases, is symptomatic and is manifested with dysphonia, dysphagia or central cervical mass, hardened and static.
  - (b) Papillary carcinoma in children is a rare disease, with frequent lymph node dissemination and low mortality rate.
  - (c) The Cytopathologic diagnosis (FNAC) for variant high-cell of follicular carcinoma is rarely diagnostic.
  - (d) Generally they are manifest Eco graphically as hyperechoic nodules, and with marked central vascularization.
  - (e) **Hürthle carcinoma (also called adenoid-cystic) was considered as a variant of follicular carcinoma some time ago.**
4. For the **thyroid micro carcinoma**, mark the incorrect statement:
- (a) **It has no extracapsular extension.**
  - (b) It is present in up to 10% of autopsies in the elderly.
  - (c) It has a surgical indication on principle.
  - (d) Low lethality.
  - (e) It can be multicentric.
5. The treatment, aiming the medullary carcinoma cure, can be done through, except:
- (a) **Partial thyroidectomy.**
  - (b) Total thyroidectomy.
  - (c) Total thyroidectomy and cervical emptying central compartment.
  - (d) Total thyroidectomy and bilateral cervical emptying.
  - (e) There are three correct alternatives.

6. Regarding the very **differentiated thyroid carcinomas**, considering the following statements, the appropriate alternative would be:
- I. PETSCAN is considered an examination of choice in metastasis research.
  - II. The segment can be performed through thyroglobulin, PCI and ultrasonography.
  - III. It is agreed that calcitonin should be routinely requested in the preoperative period of these patients.
  - IV. Recombinant TSH can be used at follow-up.
  - V. Undetectable thyroglobulin is meaningful even in the presence of antithyroglobulin antibodies.
- (a) The statements (I), (II) and (III) are correct.
  - (b) The statements (II), (IV) and (V) are wrong.
  - (c) The statements (I), (II) and (V) are correct.
  - (d) **The statements (I), (III) and (V) are wrong.**
  - (e) The statements (I), (III) and (IV) are correct.
7. In cases of papillary thyroid carcinoma with some metastatic lymph nodes detected at level VI, it is recommended to perform:
- (a) Cervical emptying of the central and lateral compartment
  - (b) **Anterior cervical dissection (central compartment)**
  - (c) Anterior cervical evacuation extended to level IV
  - (d) Suprahyoid drainage
  - (e) Do not empty
8. Choose which alternative does not represent indications of thyroid gland scintigraphy.
- (a) **differentiate a suspected carcinoma nodule with a predominantly cystic nodule**
  - (b) differentiate toxic nodular goiter with severe disease
  - (c) evaluate a specific area of the gland, such as a palpable nodule
  - (d) find ectopic thyroid tissue
  - (e) determine if a cervical or mediastinal mass has thyroid origin
9. Regarding the Thyroid Carcinoma, choose the wrong alternative:
- (a) The Papillary Carcinoma is a very differentiated, it is the most prevalent carcinoma of this gland, it can be diagnosed through Fine Needle Aspiration Biopsy (FNA) and more often generates metastases through the lymphatic route, not via hematogenous.
  - (b) **Follicular Carcinoma is a very differentiated carcinoma, it is the second most prevalent of the Carcinomas of this gland, can be diagnosed through Fine Needle Aspiration Biopsy (FNA) and more frequently generates hematogenous metastases, not lymphatic.**
  - (c) Anaplastic Carcinoma is an undifferentiated carcinoma, accounting for less than 5% Carcinomas of this gland, can be diagnosed through Fine Needle

Aspiration Biopsy (FNA) and frequently generates hematogenic rather than lymphatic metastases.

- (d) Medullar Carcinoma originates in C cells (calcitonin producers), may present in familiar or sporadic form, and may form part of the Multiple Endocrine Neoplasia type II, along with Primary Hyperparathyroidism and Pheochromocytoma.
  - (e) Galectin 3 is often positive in papillary thyroid carcinoma.
10. The treatment of thyroid medullary carcinoma, without suspicious lymph nodes in the ultrasound, is done with the accomplishment of:
- (a) partial thyroidectomy
  - (b) total thyroidectomy
  - (c) **total thyroidectomy and cervical emptying central compartment**
  - (d) total thyroidectomy and bilateral cervical emptying
  - (e) extended total thyroidectomy
11. Choose the correct option:
- (a) focus of anaplastic thyroid carcinoma in very differentiated carcinoma, certainly do not influence patient's prognosis.
  - (b) the higher incidence of anaplastic thyroid carcinoma is in the second and third decade of life
  - (c) **the lower frequency of anaplastic carcinoma also comes from the greater number of surgical procedures on the thyroid gland**
  - (d) anaplastic thyroid carcinoma is more frequent in men
  - (e) patient's death with anaplastic thyroid carcinoma usually comes from respiratory failure due to pulmonary metastases
12. Patient submitted to total and pathological lobectomy with diagnosis of micro invasive follicular carcinoma with 1 cm. The accepted procedures would be, except?
- (a) Complementary total thyroidectomy.
  - (b) Observation.
  - (c) **Dosage of stimulated thyroglobulin.**
  - (d) Dosage of anti-thyroglobulin.
  - (e) Levothyroxine suppression.
13. A 45-year-old male, submitted to total thyroidectomy for papillary carcinoma variant of oxyphilic cells of the thyroid measuring 1.5 cm and being a single lesion. What is the best choice of action below?
- (a) Cervical emptying levels II to V ipsilateral prophylactic.
  - (b) Observation and replacement of levothyroxine.
  - (c) Whole-body research with <sup>131</sup>-iodine and therapeutic dose if necessary.
  - (d) **Therapeutic dose with <sup>131</sup>-Iodine and post-dose full-body research.**
  - (e) Ablative dose of I<sup>131</sup> with 30 mCi associated with recombinant TSH.

14. Regarding the occurrence of BRAF gene mutations in very differentiated thyroid carcinomas, it is correct to state that:
- (a) It occurs in follicular carcinoma with a higher frequency.
  - (b) **It often means a worse prognosis for its patients.**
  - (c) It is a germinative mutation associated with greater local aggressiveness at the initial diagnosis.
  - (d) There are no other activating mutations described for this oncogene yet.
  - (e) When it occurs, it activates the caspase pathway, known mechanism of cell death.
15. The medullary carcinoma has molecular origin:
- (a) In BRAF mutation
  - (b) In RET-PTC mutation
  - (c) **In RET proto-oncogene mutation**
  - (d) In nuclear membrane
  - (e) None of the above

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# Chapter 33

## Parotid Gland Tumors



José Aurillo Rocha and Ramon Andrade De Mello

**Abstract** The parotid glands are the largest salivary glands in humans and are frequently involved in disease processes. Approximately 25% of parotid masses are nonneoplastic; the remaining 75% are neoplastic. Anatomically, the parotid gland is the most frequent site of salivary gland tumors, accounting for approximately 80–85% of these tumors. Approximately three-fourths of parotid lesions are benign, and approximately 25% are malignant.

**Keywords** Parotid Gland Tumors · Chemotherapy · Radiotherapy

### 33.1 Introduction and Anatomy

The parotid glands are the largest salivary glands in humans and are frequently involved in disease processes. Approximately 25% of parotid masses are nonneoplastic; the remaining 75% are neoplastic. Anatomically, the parotid gland is the most frequent site of salivary gland tumors, accounting for approximately 80–85% of these tumors. Approximately three-fourths of parotid lesions are benign, and approximately 25% are malignant.

Nonneoplastic causes of parotid enlargement include cysts, [parotitis](#), lymphoepithelial lesions associated with AIDS, collagen vascular diseases, and benign hypertrophy. Benign hypertrophy is encountered in patients with [bulimia](#), [sarcoidosis](#), sialosis, [actinomycosis infections](#), and [mycobacterial infections](#). The vast majority (approximately 80%) of parotid neoplasms are benign; these are discussed in detail in the Medscape Drugs & Diseases article [Benign Parotid Tumors](#).

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The paired parotid glands are formed as epithelial invaginations into the embryological mesoderm and first appear at approximately 6 weeks gestation. The glands are roughly pyramidal in shape, with the main body overlying the masseter muscle.

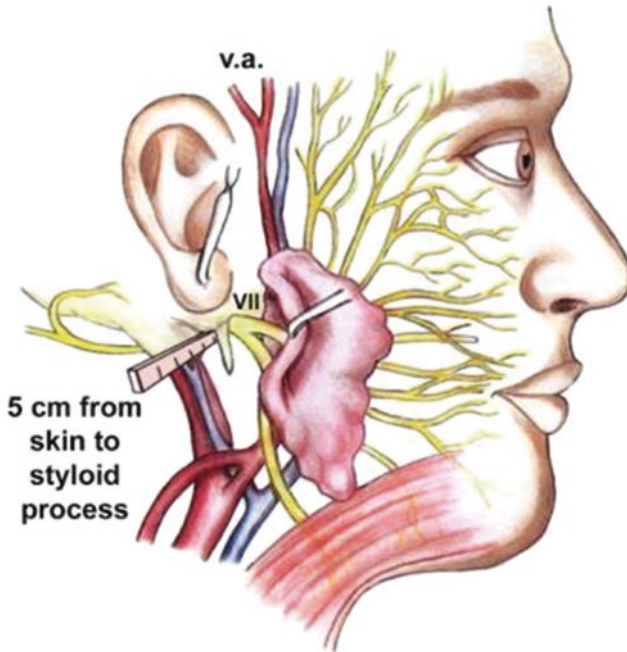
The glands extend to the zygomatic process and mastoid tip of the temporal bone and curve around the angle of the mandible to extend to the retromandibular and parapharyngeal spaces. The parotid duct exits the gland medially, crosses the superficial border of the masseter, pierces the buccinator, and enters the oral cavity through the buccal mucosa opposite the second maxillary molar.

The gland is divided into a superficial and deep portion by the facial nerve, which passes through the gland. While not truly anatomically discrete, these “lobes” are important surgically, as neoplasms involving the deep lobe require sometimes significant manipulation of the facial nerve to allow excision. The superficial lobe is the larger of the two and thereby the location of the majority of parotid tumors.

The facial nerve exits the cranium via the stylomastoid foramen and courses through the substance of the parotid gland. The superficial lobe of the parotid lies superficial or lateral to the facial nerve, whereas the deep lobe is deep or medial to the facial nerve. The facial nerve branches within the substance of the parotid gland, and the branching pattern can be highly variable. The main trunk typically bifurcates into the zygomaticotemporal branch and the cervicofacial branch at the pes anserinus, also known as the goose’s foot (see images below), and thereafter into the temporal, zygomatic, buccal, marginal, and cervical branches. Pes is about 1.3 cm from the stylomastoid foramen. Extensive anastomoses are usually present between branches of the zygomatic and buccal branches of the nerve.



The (Z) zygomaticotemporal branch and the (C) cervicofacial branch of the facial nerve are dissected out during resection of a parotid tumor. The pes (goose’s foot) is visible in this photograph.



The surgical anatomy and landmarks of the facial nerve.

### 33.2 Diagnosis

Evaluation of a patient with a suspected parotid gland malignancy must begin with a thorough medical history and physical examination.

The most common presentation is a painless, asymptomatic mass; >80% of patients present because of a mass in the posterior cheek region. Approximately 30% of patients describe pain associated with the mass, though most parotid malignancies are painless. Pain most likely indicates perineural invasion, which greatly increases the likelihood of malignancy in a patient with a parotid mass.

Of patients with malignant parotid tumors, 7–20% present with facial nerve weakness or paralysis, which almost never accompanies benign lesions and indicates a poor prognosis. Approximately 80% of patients with facial nerve paralysis have nodal metastasis at the time of diagnosis. These patients have an average survival of 2.7 years and a 10-year survival of 14–26%.

Other important aspects of the history include length of time the mass has been present and history of prior cutaneous lesion or parotid lesion excision. Slow-growing masses of long-standing duration tend to be benign. A history of prior squamous cell carcinoma, malignant melanoma, or malignant fibrous histiocytoma



suggests intraglandular metastasis or metastasis to parotid lymph nodes. Prior parotid tumor most likely indicates a recurrence because of inadequate initial resection.

Trismus often indicates advanced disease with extension into the masticatory muscles or, less commonly, invasion of the temporomandibular joint. **Dysphagia** or a sensation of a foreign body in the oropharynx indicates a tumor of the deep lobe of the gland. A report of ear pain may indicate extension of the tumor into the auditory canal. The presence of numbness in the distribution of the second or third divisions of the trigeminal nerve often indicates neural invasion.

Physical examination of the head and neck must be thorough and complete. The entire head and neck must be examined for cutaneous lesions, which may represent malignancies that could metastasize to the parotid gland or parotid nodes.

- Palpation of the mass should determine the degree of firmness. Even benign tumors are usually firm, but a rock-hard mass generally denotes malignancy.
- Skin fixation, skin ulceration, or fixation to adjacent structures also indicates malignancy. The external auditory canal must be visualized for tumor extension.
- All regional nodes must be carefully palpated to detect nodal metastasis. Examination of the oral cavity and oropharynx also may yield further evidence of metastasis or malignant nature of the lesion.
- Blood or pus from the Stenson duct is a sign of malignancy but is infrequently encountered. More often, one may see bulging of the lateral pharyngeal wall or soft palate, indicating tumor in the deep lobe of the gland.
- Bimanual palpation with one finger against the lateral pharyngeal wall and the other against the external neck may confirm extent into the tonsillar fossa and soft palate.

Once a thorough history and physical examination are complete, perform diagnostic procedures to confirm the diagnosis and extent of the disease process.

### 33.3 Fine Needle Aspiration

See the list below:

- Fine needle aspiration of the mass or an enlarged lymph node may be performed to obtain a tissue diagnosis [1]. Most surgeons recommend excision of a parotid mass whether it is benign or malignant unless a patient's comorbidity precludes safe surgery. As such, many surgeons do not routinely perform cytology before proceeding with surgery.
- The sensitivity of this procedure is greater than 95% in experienced hands. However, only a positive diagnosis should be accepted; negative results indicate the need for further attempts at obtaining a histologic diagnosis, including repeat fine needle aspiration.

- The results of the fine needle aspiration provide a histologic diagnosis and assist in preoperative planning and patient counseling. It may not distinguish benign from malignant epithelial lesions because malignancy of parotid epithelial cells is related to the behavior of the tumor cells in relation to tissue planes and surrounding structures rather than cellular architecture, which may be rather normal even in malignancy. Therefore, nonepithelial lesions may be diagnosed with accuracy, but epithelial lesions may require further investigation.
- If fine needle aspiration is unsuccessful in obtaining a diagnosis, an incisional biopsy should not be performed. This procedure has a high rate of local recurrence and places the facial nerve at risk for injury from inadequate visualization.
- Some authors advocate large core needle biopsies, but this procedure is less popular because of potential facial nerve injury and the possibility of seeding the needle tract with tumor cells.
- If a core biopsy is performed, the needle should be inserted so that the tract may be excised during the definitive operation. When all attempts at obtaining a histologic diagnosis have failed, operative exploration should proceed after appropriate imaging studies have been obtained.
- Intraoperatively, a frozen section of the specimen should be submitted for diagnosis. The use of frozen sections has demonstrated greater than 93% accuracy in the diagnosis of parotid malignancy.

### 33.4 Epidemiology and Risk Factors

Salivary gland tumors are rare, representing only 6–8% of head and neck tumors; in the United States, there are approximately 2000 to 2500 cases per year [1, 2]. There are substantial geographic variations in the incidence of salivary gland tumors and in the types of tumors in a given area.

- Although there is no one predominant factor known to be associated with the development of salivary gland cancer, a number of factors have been implicated as potential causes:
- Radiation exposure has been associated with the development of both benign and malignant salivary gland tumors. This relationship was initially based upon data from atomic bomb survivors in Japan [3]. There also appears to be an increased risk in long-term cancer survivors who received radiation therapy as part of their treatment for Hodgkin lymphoma [4, 5] and in individuals who received radiation to the head and neck region for childhood cancers or benign conditions [6, 7]. Those with a prior history of Hodgkin lymphoma may be at risk of onset of a salivary cancer at a younger-than-typical age for this malignancy [5].
- Warthin tumor has a strong association with smoking, in contrast to other salivary gland tumors for which there is no clear relationship. Although this benign tumor has been historically associated with older men, the incidence in women has increased and parallels the increased smoking rates of women [1, 8, 9].

- Viral infections may be associated with an increased risk of salivary gland cancers.
  - Epstein Barr virus (EBV) – Lymphoepithelial carcinoma is an undifferentiated carcinoma that accounts for less than 1% of salivary gland tumors; lymphoepithelial carcinoma has been strongly associated with EBV in areas where EBV is endemic [1].
  - Human immunodeficiency virus (HIV) – Epidemiologic studies have reported an increased incidence of these tumors in individuals infected with HIV [10, 11].
  - Human papillomavirus (HPV) – While high-risk serotypes [12, 13] of HPV have occasionally been detected in mucoepidermoid carcinoma [14, 15], others have not confirmed this observation [16], and it has only rarely been detected in other salivary cancers [17–19]. There are no conclusive data that support a causative role for HPV in the etiology of salivary gland cancers.
- Environmental factors and industrial exposure to factors such as rubber manufacturing, hair dressers, beauty shops, and nickel compounds have been reported to be associated with the development of salivary gland tumors [2, 20].

### 33.5 Pathology

Many types of parotid malignancies exist, most arising from the epithelial elements of the gland [3, 21–24]. Classification of these tumors can be quite confusing. In addition, malignancy may develop in the secretory element of the gland or malignancy arising elsewhere may first be noticed as a metastasis to the gland.

### 33.6 Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common malignant tumor of the parotid gland, accounting for 30% of parotid malignancies [4, 5].

Three cell types are found in varying proportions: mucous, intermediate, and epidermoid cells. High-grade tumors exhibit cytologic atypia, higher mitotic frequency, areas of necrosis and more epidermoid cells. High-grade tumors behave like a squamous cell carcinoma; low-grade tumors often behave similar to a benign lesion [6].

Limited local invasiveness and low metastatic potential characterize this tumor, particularly when cytologically low-grade. If metastatic, it is most likely to metastasize to regional nodal basins rather than to distant locations.

For patients with low-grade tumors without nodal or distant metastasis, 5-year survival is 75–95%, whereas patients with high-grade tumors with lymph node metastasis at the time of diagnosis have a 5-year survival of only 5%. Overall 10-year survival is 50%.

Differential diagnosis includes chronic sialoadenitis, [necrotizing sialometaplasia](#), and other carcinomas. An association has been reported between mucoepidermoid carcinoma and [myasthenia gravis](#) [7].

### 33.7 Adenoid Cystic Carcinoma

The adenoid cystic carcinoma is characterized by its unpredictable behavior and propensity to spread along nerves. It possesses a highly invasive quality but may remain quiescent for a long time.

This tumor may be present for more than 10 years and demonstrate little change and then suddenly infiltrate the adjacent tissues extensively.

The tumor has an affinity for growth along perineural planes and may demonstrate skip lesions along involved nerves. Clear margins do not necessarily mean that the tumor has been eradicated.

Metastasis is more common to distant sites than to regional nodes; lung metastases are most frequent. This tumor has the highest incidence of distant metastasis, occurring in 30–50% of patients.

Three histologic types have been identified: cribriform, tubular, and solid. The solid form has the worst prognosis; the cribriform pattern possesses the most benign behavior and best prognosis. This tumor requires aggressive initial resection. Overall 5-year survival is 35%, and 10-year survival is approximately 20%.

### 33.8 Malignant Mixed Tumors

Malignant mixed tumors arise most commonly as a focus of malignant degeneration within a preexisting benign pleomorphic adenoma (carcinoma ex pleomorphic adenoma).

These tumors also may develop de novo (carcinosarcoma). The longer pleomorphic adenoma has been present, the greater the chance of carcinomatous degeneration.

Carcinosarcomas, true malignant mixed tumors, are rare. Overall 5-year survival is 56%, and 10-year survival is 31%.

### 33.9 Acinic Cell Carcinoma

Acinic cell carcinoma is an intermediate-grade malignancy with low malignant potential. This tumor may be bilateral or multicentric and is usually solid, rarely cystic.

Although this tumor rarely metastasizes, occasional late distant metastases have been observed. This tumor also may spread along perineural planes. Overall 5-year survival is 82%, and 10-year survival is 68%.

### **33.10 Adenocarcinoma**

Adenocarcinoma of the parotid develops from the secretory element of the gland. This is an aggressive lesion with potential for both local lymphatic and distant metastases.

Approximately 33% of patients have nodal or distant metastasis present at the time of initial diagnosis. Overall 5-year survival is 19–75%, as it is highly variable and related to grade and stage at presentation.

A study by Zhan and Lentsch of basal cell adenocarcinoma of the major salivary glands (509 cases) found that 88% of tumors were in the parotid glands, with 11.2% in the submandibular glands and 0.8% being sublingual gland lesions. Overall 5- and 10-year survival rates were 79% and 62%, respectively, while regional and distant metastases occurred in just 11.9% and 1.8% of cases, respectively. Older age (65 years or older) and high primary tumor stage had a significant negative impact on survival; in patients with a high tumor stage, the survival rate was significantly better with a combination of surgery and radiation therapy than with surgery alone [8].

### **33.11 Primary Squamous Cell Carcinoma**

Primary squamous cell carcinoma of the parotid is rare, and metastasis from other sites must be excluded. Overall 5-year survival is 21–55%, and 10-year survival is 10–15%.

### **33.12 Sebaceous Carcinoma**

**Sebaceous carcinoma** is a rare parotid malignancy that often presents as a painful mass. It commonly involves the overlying skin.

### **33.13 Salivary Duct Carcinoma**

Salivary duct carcinoma is a rare and highly aggressive tumor. Small cell carcinoma exists as 2 types. The ductal cell origin type is mostly benign and rarely metastasizes. The neuroendocrine origin type is often aggressive and has higher metastatic potential.

### **33.14 Lymphoma**

The parotid gland also may be the site of occurrence of lymphoma, most commonly in elderly males. This is also observed in approximately 5–10% of patients with Warthin tumor of the parotid gland, a benign neoplasm [9].

The entire parotid is typically enlarged with a rubbery consistency on palpation. Often, regional nodes also are enlarged. Biopsy of enlarged regional nodes avoids unnecessary parotid surgery, as the definitive treatment consists of chemotherapy or radiation therapy.

### **33.15 Malignant Fibrohistiocytoma**

Malignant fibrohistiocytoma is very rare in the parotid gland. It presents as a slow growing and painless mass.

Fine needle aspiration and imaging could confuse this lesion with other kinds of parotid tumors; therefore, definite diagnosis should be based on immunohistochemical analysis of the resected tumor. The tumor should be completely resected [10].

### **33.16 Parotid Metastasis from Other Sites**

The parotid also may be the site of metastasis from cutaneous, renal, lung, breast, prostate, or GI tract malignancies.

### **33.17 Operative Management**

Generally, therapy for parotid malignancy is complete surgical resection followed, when indicated, by radiation therapy [11]. Conservative excisions are plagued by a high rate of local recurrence. The extent of resection is based on tumor histology, tumor size and location, invasion of local structures, and the status of regional nodal basins.

Most tumors of the parotid (approximately 90%) originate in the superficial lobe. Superficial parotid lobectomy is the minimum operation performed in this situation. This procedure is appropriate for malignancies confined to the superficial lobe, those that are low grade, those less than 4 cm in greatest diameter, tumors without local invasion, and those without evidence of regional node involvement.

### 33.18 Surgical Resection Procedure

The most important initial step is identification of the facial nerve and its course through the substance of the parotid gland. In order to preserve the facial nerve, it is important to try to determine the proximity of the nerve to the capsule of the tumor prior to surgery. Results of a retrospective review showed that malignant tumors were likely to have a positive facial nerve margin [12]. Virtually all surgeons avoid using paralytic agents, and, to assist finding the nerve, many surgeons use a nerve stimulator. Increasingly, surgeons are using intraoperative continuous facial nerve monitoring any time a parotidectomy is performed. This is not usually necessary in the primary setting, but recurrent resections may be very difficult and probably should be performed using this device.

- Ideally, the dissection of the facial nerve should be performed without disturbing or violating the tumor. The facial nerve may be found exiting the stylomastoid foramen by reflecting the parotid gland anteriorly and the sternocleidomastoid muscle posteriorly. Landmarks include the digastric ridge and the tympanomastoid suture. Knowledge of the relationships among these structures allows more efficient and reproducible identification of the nerve.
- The cartilaginous external auditory canal lies approximately 5 mm superior to the facial nerve in this region. The facial nerve is also anterior to the posterior belly of the digastric muscle and external to the styloid process.
- A second technique for locating the facial nerve is to identify a distal branch of the nerve and to dissect retrograde toward the main trunk. This technique may be more difficult depending on the ease of identifying the branching pattern. To perform this maneuver, the buccal branch may be found just superior to the parotid duct, or the marginal mandibular branch may be found crossing over (superficial to) the facial vessels. These may then be traced back to the origins of the main facial nerve trunks.
- A final way of identifying the nerve in particularly difficult situations is to drill the mastoid and to locate the nerve within the temporal bone. It may then be followed through the stylomastoid foramen antegrade towards the parotid.
- Once these have been identified, the superficial lobe of the parotid gland may be removed en bloc and sent to the pathology laboratory.
- If the immediate intraoperative pathologic examination reveals that the tumor is actually high-grade or >4 cm in greatest diameter, or lymph node metastasis is identified within the specimen, a complete total parotidectomy should be performed.
- If the facial nerve or its branches are adherent to or directly involved by the tumor, they must be sacrificed. However, a pathologic diagnosis of malignancy must be confirmed intraoperatively prior to sacrificing facial nerve branches.
- All involved local structures should be resected in continuity with the tumor. This may include skin, masseter, mandible, temporalis, zygomatic arch, or temporal bone.

- Tumors of the deep lobe are treated by total parotidectomy. Identification of the facial nerves and branches is the first and most crucial step.
- Total parotidectomy is then performed en bloc, and the fate of the facial nerve and surrounding local structures must be decided similar to superficial lobe tumors. The specimen should be sent to the pathology laboratory for immediate examination.
- Neck dissection should be performed when malignancy is detected in the lymph nodes pre- or intraoperatively.
- Other indications for functional neck dissection include tumors >4 cm in greatest diameter, tumors that are high-grade, tumors that have invaded local structures, recurrent tumors when no neck dissection was performed initially, and deep lobe tumors.
- These recommendations are based on the higher likelihood of occult, clinically undetectable nodal disease present at the time of operation in patients whose tumors display the above characteristics.

### 33.19 Adjunctive Therapy

Patients with a tumor of a major salivary gland typically present with a painless mass or swelling of the parotid, submandibular, or sublingual gland. The presence of a parotid mass in combination with signs or symptoms indicative of facial nerve involvement (e.g., facial nerve paralysis) is generally indicative of a malignant rather than a benign tumor.

Because of the many histologic subtypes of parotid malignancies, a general statement regarding the usefulness of adjunctive therapy cannot be made.

If resectable, surgery is the primary modality of treatment for most malignant tumors of the parotid gland. General indications for postsurgical radiation therapy include tumors >4 cm in greatest diameter, tumors of high grade, tumor invasion of local structures, lymphatic invasion, neural invasion, vascular invasion, tumor present very close to a nerve that was spared, tumors originating in or extending to the deep lobe, recurrent tumors following re-resection, positive margins on final pathology, and regional lymph node involvement. Postoperative radiation is, thus, usually indicated for all parotid malignancies with the exception of small low-grade tumors with no evidence of local invasion or nodal/distant spread. Radiation therapy is considered the cornerstone of adjunctive therapy.

No chemotherapy has been proven effective as single modality therapy. For certain histologic subtypes, some clinicians recommend combined modality chemotherapy and radiation. Presently, immunotherapy is in the clinical trial phase.

A recent study demonstrated that epidermal growth factor receptor (EGFR) is expressed strongly in the cell membranes of parotid mucoepidermoid carcinomas and of the lymph node metastases [15]. EGFR-targeting agents have potential to be used for therapy.



### 33.20 Differential Diagnosis

A wide range of pathologic processes can cause a salivary gland mass or enlargement. In addition to benign and malignant tumors, the differential diagnosis of patients includes salivary cysts, cysts of the first branchial cleft, salivary gland stones, sarcoid, Sjögren syndrome, metastases from other tumors, lymphoepithelial cysts (particularly in an immunocompromised host), chronic sclerosing sialadenitis (Küttner tumor), and regional lymphadenopathy from infectious, inflammatory, or malignant diseases. Distinguishing among these possibilities may require a tissue diagnosis. (See “[Differential diagnosis of a neck mass](#)”.)

In patients presenting with facial nerve palsy, a high suspicion of malignant involvement of the parotid gland must be entertained in those with a history of skin cancer or melanoma of the scalp or face, as well as in those with a history of removal of a skin lesion that was not sent for pathologic examination.

A malignant parotid tumor must be distinguished from Bell palsy. Patients with apparent Bell palsy require further evaluation if there are other neurologic abnormalities, there are features on physical examination that suggest a parotid tumor, or there is no evidence of improvement within a reasonable time frame.

Other rare causes of facial nerve paralysis that must be distinguished from a parotid tumor include sarcoid infiltration of the parotid gland (known as Heerfordt syndrome) and intraparotid facial nerve schwannoma.

Malignancies of the parotid, submandibular, and sublingual glands are staged according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) system. Tumors arising in minor salivary glands are staged according to their anatomic site of origin. Imaging studies using computed tomography (CT), magnetic resonance imaging (MRI), and in some cases positron emission tomography (PET) may provide important information about the extent of local invasion or dissemination.

### 33.21 Prognosis

The major determinants of survival are histology and clinical stage. Poor prognostic factors include high grade, neural involvement, locally advanced disease, advanced age, associated pain, regional lymph node metastases, distant metastasis, and accumulation of p53 or c-erbB2 oncoproteins [16–19].

Although statements regarding survival are difficult to make because of the large variety of histologic types, 20% of all patients will develop distant metastases [25]. The presence of distant metastases heralds a poor prognosis, with a median survival of 4.3–7.3 months.

Overall 5-year survival for all stages and histologic types is approximately 62%. The overall 5-year survival for recurrent disease is approximately 37%. Because of

the risk of recurrence, all patients who have had a histologically proven malignant salivary gland tumor should have lifelong follow-up.

A study by Kim et al. of 126 patients treated for primary parotid cancer found the following disease-specific survival rates for the various tumor stages (mean follow-up period 29.7 months):

- Stage I (97%)
- Stage II (81%)
- Stage III (56%)
- Stage IV (15%)

Patients in the study underwent superficial, total, or radical parotidectomy, with 57 also undergoing postoperative radiotherapy. Fifteen patients (12%) experienced disease recurrence.

### 33.22 Surveillance

Surveillance must continue indefinitely, as local recurrence or distant metastases may become apparent many years after the initial treatment.

The patient should undergo a thorough physical examination every 3 months for 2 years, every 6 months for another 3 years, then annually thereafter. Liver function tests and chest radiograph should be obtained annually.

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# Chapter 34

## Melanoma



Antonio Maria Grimaldi and Paolo Antonio Ascierto

**Abstract** Melanoma is a malignant tumor that arises from melanocytic cells and primarily involves the skin. Early diagnosis is fundamental for surgical treatment of localized disease. A conservative surgical excision approach is favored with the extent based on the Breslow thickness. The search for the sentinel lymph node is fundamental for surgical staging, with risk of lymph node involvement directly proportional to thickness of the primary melanoma or the presence of mitosis. Complete lymph node dissection is indicated for metastases to clinically evident regional lymph nodes. Adjuvant systemic therapy is primarily interferon- $\alpha$  while new immunomodulating antibodies and targeted therapies may offer new options. When melanoma is unresectable or metastatic, immunotherapy and targeted therapy can have a significant impact on prognosis. Since 2011, the emergence of new immunomodulating and molecular targeted drugs has resulted in significant improvements in survival for patients with metastatic disease. In particular, the introduction of anti-CTLA-4 (ipilimumab) and anti-PD-1 immunotherapies (nivolumab, pembrolizumab) has been major turning point. The availability of new immunotherapies and targeted therapies has led to various combination regimens to further improve patient outcomes. Future developments will involve novel combinations that overcome resistance and/or reduce toxicity compared to current options.

**Keywords** Melanoma · Surgery · Sentinel node · Immunotherapy · Targeted therapy · Combination therapy

### Abbreviations

CLND complete lymph node dissection  
CSD chronic sun damage

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CTLA-4	cytotoxic T-lymphocyte-associated antigen
DFS	disease-free survival
HDI	high-dose interferon
HR	hazard ratio
IFN	interferon
LAG	lymphocyte activation gene
LDH	lactate dehydrogenase
LDI	low-dose interferon
MAPK	mitogen-activated protein kinase
ORR	objective response rate
OS	overall survival
PD-1	programmed death-1
PFS	progression-free survival
RFS	relapse-free survival
TRAEs	treatment-related adverse events
UNL	upper normal limit

### 34.1 Introduction

Melanoma is a malignant tumor that arises from melanocytic cells and primarily involves the skin. Early diagnosis is fundamental for surgical treatment of localized disease. When melanoma is unresectable or metastatic, immunotherapy and targeted therapy can have a significant impact on prognosis.

### 34.2 Diagnosis and Prognostic Factors

Two main categories of melanomas are generally recognized, those typically associated with chronic sun damage (CSD), and melanomas generally not associated with CSD [1]. More recently, molecular alterations associated with melanoma have been identified, especially in genes involved in the mitogen-activated protein kinase (MAPK) pathway responsible for regulating proliferation, invasion and cell survival processes. Four distinct molecular subtypes have been identified: mutations activating the BRAF gene, mutations activating RAS genes (including N-RAS), inactivating mutation of the NF1 gene (which determines functional activation of RAS genes), and no mutations in these three genes (triple wild-type) [2].

In general, about 50% of melanomas have mutations affecting the BRAF gene [3]. Mutations in the NRAS gene are observed in 15–20% of cutaneous melanomas. Although NRAS is not a therapeutic target, the identification of mutations is clinically relevant as recent evidence has demonstrated the efficacy of MEK inhibitors in patients with NRAS-mutated melanoma [4]. Since mutations of BRAF and NRAS are usually mutually exclusive, assessing NRAS mutational

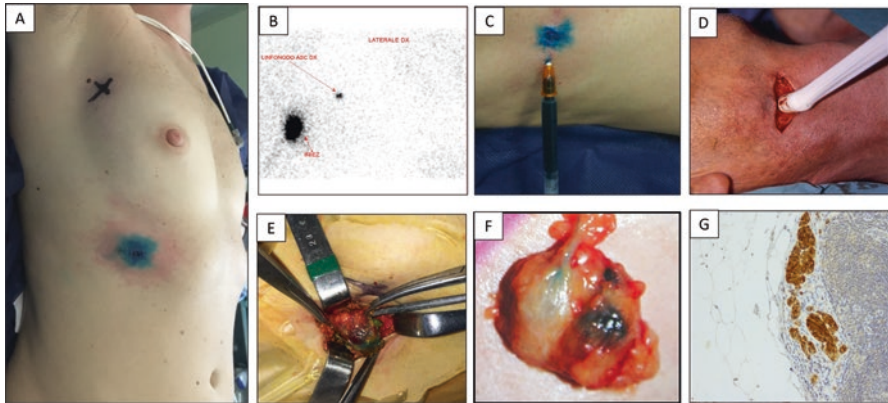
status is indicated in the absence of BRAF mutations in patients with inoperable or metastatic melanoma [5]. Mutations of the c-KIT gene are observed in 1–3% of melanomas, with greater frequency in mucosal and acral melanomas (15–20%) [6]. In wild-type BRAF and NRAS melanomas, mutations of the c-KIT gene should be evaluated [7].

### 34.3 Treatment Approaches

#### 34.3.1 Surgery of Primary Melanoma

A conservative excision approach is favored with the extent based on the Breslow thickness. Excision with less extensive margins may be justified in case of severe aesthetic-functional impairment, although patients require close post-surgical monitoring.

The search for the sentinel lymph node is fundamental for surgical staging [8] (Fig. 34.1). The risk of lymph node involvement is directly proportional to the Breslow thickness of the primary melanoma or the presence of mitosis [9]. In a melanoma with a thickness < 1 mm, lymph nodal metastases are rare, while for melanomas with a thickness of 1.5–4 mm, involvement is verified in 25%, rising to



**Fig. 34.1** Lymphatic mapping and SLN concept and technique

The SLN concept is illustrated demonstrating potential afferent drainage patterns from primary tumor sites to the first draining nodes (sentinel node) in the regional basins in (a). Lymphoscintigraphy (b) identifies nodal basin(s) at risk for primary melanomas arising in the lymphatic drainage sites and the number sentinel nodes in the basin. In panel B, lymphatic drainage from the low back is to the axilla rather than the closer inguinal basin. Injection of isosulfan blue intradermally around biopsy site in (c), Transcutaneous localization of SLN using gamma detection probe in (d), exploration of nodal basin and visualization of SLN in (e) and (f) and histologic detection of occult metastases in subcapsular sinus in (g)

Ross, MI. Sentinel Node Biopsy for Melanoma: An Update After Two Decades of Experience. *Semin Cutan Med Surg* 2010, 29:238–248

60% for melanoma with thickness  $\geq 4$  mm [10]. Sentinel lymph node biopsy should be offered to all patients who have a primary melanoma with thickness  $> 1$  mm, regardless of other histopathological features, or in pT1b melanomas. In particular, it is recommended in patients with intermediate-risk lesions (thickness 1–4 mm). It may also be useful in thick melanomas ( $>4$  mm) for more accurate staging and to facilitate locoregional disease control. Melanoma is staged using the TNM classification as described by the latest review of the American Joint Committee on Cancer (AJCC), 8th edition (Table 34.1).

Complete lymph node dissection (CLND) is indicated only for metastases to clinically evident regional lymph nodes [11]. In a phase III study in 1934 patients with positive sentinel lymph node biopsy, CLND compared to observation alone was not associated with a significant improvement in melanoma-specific survival at a median 3 years follow-up [12]. In patients with macrometastases, assessing the presence of BRAF, NRAS and/or c-KIT mutations is recommended [13].

## 34.4 Medical Treatment

### 34.4.1 Adjuvant Therapy

Interferon (IFN)- $\alpha$  has been, and in many countries is still, the only available adjuvant therapy for melanoma patients with high risk of relapse and is associated with improved event-free survival, relapse-free survival (RFS) and overall survival (OS) [14]. The ideal dose, most advantageous schedule and optimal duration in the intermediate-high risk melanoma patient has not been identified. In stage I disease, IFN is not recommended given the potential for good prognosis. For IIA disease, observation is recommended in patients with a good prognosis, reserving treatment with low-dose IFN (LDI) for 18 months in patients with worse prognosis (high mitotic index, thickness  $> 1.5$  mm, male, localization to the back or head and neck) [15]. In stage IIC-IIIB, treatment with LDI or high-dose IFN (HDI) can be considered based on patient characteristics and clinical experience. In IIIC disease, treatment with HDI is preferable.

#### 34.4.1.1 New Options in Adjuvant Therapy

The efficacy of adjuvant therapy with ipilimumab, a monoclonal antibody directed against the cytotoxic T-lymphocyte-associated antigen (CTLA)-4 receptor, has been assessed in the phase III EORTC 18071 study in stage III melanoma [16]. This compared ipilimumab 10 mg/kg (every 3 weeks for a 4-cycle induction phase followed by single administration every 12 weeks for an up to 3-year maintenance phase) versus placebo in 951 patients. Ipilimumab demonstrated an improvement in median RFS (26.1 vs. 17.1 months; hazard ratio [HR] 0.75 [95% CI 0.64–0.90]).

**Table 34.1** Melanoma staging according to AJCC (8th edition)

<i>T category</i>	<i>Breslow thickness<sup>a</sup></i>	<i>Ulceration</i>
<b>T1 ≤ 1,0 mm</b>		
T1a	a: <0,8 mm	Absent
T1b	b: <0,8 mm	Present
	0,8–1,0 mm	Absent/present
<b>T2 &gt; 1,0–2,0 mm</b>		
T2a	a: >1,0–2,0 mm	Absent
T2b	b: >1,0–2,0 mm	Present
<b>T3 &gt; 2,0–4,0 mm</b>		
T3a	a: >2,0–4,0 mm	Absent
T3b	b: >2,0–4,0 mm	Present
<b>T4 &gt; 4,0 mm</b>		
<b>T4a</b>	a: > 4,0 mm	Absent
<b>T4b</b>	b: > 4,0 mm	Present
<i>N<sup>b</sup> category</i>	<i>N<sup>o</sup> of regional involved lymph nodes</i>	<i>In-transit metastases, satellitosis, and/or microsatellitosis<sup>c</sup></i>
N1	1 involved lymph node or in-transit metastasis, satellites, and/or microsatellitosis in the absence of regional lymph nodes involved	
N1a	a: 1 clinically occult lymph node (diagnosed with sentinel lymph node biopsy)	a: Absent
N1b	b: 1 clinically proven lymph node	b: Absent
N1c	c: Regional lymph nodes not involved	c: Present
N2	2–3 involved lymph nodes or in-transit metastases, satellites, and/or microsatellitosis with 1 regional lymph node involved	
N2a	a: 2 or 3 clinically occult lymph nodes (diagnosed with sentinel lymph node biopsy)	a: Absent
N2b	b: 2 or 3 lymph nodes, of which at least 1 is clinically proven	b: Absent
N2c	c: 1 clinically occult lymph node or clinically diagnosed	c: Present
<i>Categoria N<sup>b</sup></i>	<i>N<sup>o</sup> of regional involved lymph nodes</i>	<i>In-transit metastases, satellitosis, and/or microsatellitosis<sup>c</sup></i>
N3	4 or more involved lymph nodes or in-transit metastases, satellites, and/or microsatellitosis with 2 or more regional lymph nodes involved or any number of lymph node packets (confluent lymph nodes) with or without transit metastases, satellites and/or microsatellitosis	
N3a	a: 4 or more clinically occult lymph nodes (diagnosed with sentinel lymph node biopsy)	a: Absent

(continued)



**Table 34.1** (continued)

N3b	b: 4 or more lymph nodes, of which at least 1 is clinically proven or the presence of lymph node packs (confluent lymph nodes), in any number	b: Absent	
N3c	c: 2 or more clinically occult or clinically diagnosed lymph nodes and/or presence of lymph node packs (confluent lymph nodes), in any number	c: Present	
<b>M category</b>	<b>Anatomic site</b>	<b>LDH</b>	
M1	Evidence of distant metastasis		
M1a	a: Remote metastasis to the skin, soft tissues including muscle and/or non-regional lymph nodes		
M1a(0)		Non elevated	
M1a(1)		Elevated	
M1b	b: Remote lung metastasis with or without disease sites M1a	Not evaluated or not specified	
M1b(0)		Non elevated	
M1b(1)		Elevated	
M1c	c: Remote metastasis to visceral sites other than CNS with or without disease sites M1a or M1b	Not evaluated or not specified	
M1c(0)		Non elevated	
M1c(1)		Elevated	
M1d	d: Remote CNS metastasis with or without disease sites M1a, M1b or M1c	Not evaluated or not specified	
M1d(0)		Non elevated	
M1d(1)		Elevated	
<b>T</b>	<b>N</b>	<b>M</b>	<b>pTNM</b>
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N2c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥ N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

(continued)

**Table 34.1** (continued)

<sup>a</sup>In the most recent edition of the AJCC Staging System (eighth edition), the Breslow thickness must be rounded to the nearest tenth of a millimeter (0.1 mm) (for example, melanomas of thickness between 0.75 and 0.84 must be reported with a thickness of 0.8 mm or melanomas of thickness between 0.95 mm and 1.04 mm must be reported with a thickness of 1.0 mm). Tx indicates thickness according to non-evaluable Breslow, T0 indicates the non-evidence of a primary tumor (patient presenting with lymph node metastasis in the absence of recognized primary melanoma) while Tis indicates an in situ melanoma

<sup>b</sup>The term “micrometastasis” or “macrometastases” is no longer used, while referring to “clinically occult” or “clinically documented” disease. It is emphasized that the burden of disease (so-called “tumor burden”) in the sentinel node is not used for the sub-classification of category N

<sup>c</sup>Satellitosis are defined as clinically localized cutaneous and/or subcutaneous metastases within 2 cm of primitive melanoma. The in transit metastases are defined as clinically evident dermal and/or subcutaneous metastases at a distance >2 cm from the primary melanoma, in the region between the primary tumor and the first basin of loco-regional lymph nodes

However, treatment was associated with immune-related toxicity and 52% of patients had to discontinue due to treatment-related adverse events (TRAEs). Five toxicity-related deaths were recorded (1.1%). In a subsequent update, 5-year OS was 65.4% in the ipilimumab arm versus 54.4% in the placebo arm (HR = 0.72; 95.1% CI: 0.58–0.88;  $p = 0.001$ ) [17]. Adjuvant treatment with ipilimumab has been approved for stage III disease in the US, but it is not approved for this indication in Europe.

Recently, the Checkmate-238 study of 906 patients receiving immunotherapy after radical excision reported 12-month RFS of 70.5% (95% CI 66.1–74.5) with the anti-programmed death (PD)-1 agent nivolumab (3 mg/kg every 2 weeks) and 60.8% (95% CI 56.0–65.2) with ipilimumab (10 mg/kg every 3 weeks for 4 doses and then every 12 weeks) with a HR 0.65 (97.56% CI 0.51–0.83,  $p < 0.001$ ) [18]. The incidence of grade 3–4 TRAEs was 14.4% with nivolumab and 45.6% with ipilimumab. Early treatment discontinuation rates were 9.7% and 42.6% in the nivolumab and ipilimumab arms. OS data are not yet available.

Adjuvant studies of targeted therapy have also been reported in patients with BRAF-mutated melanoma. In the phase III COMBI-AD study, 870 patients were randomized to receive dabrafenib plus trametinib for 12 months or placebo after radical surgery [19]. At a minimum follow-up of 2.5 years, 3-year RFS was 58% in the combination group versus 39% with placebo (HR 0.47, 95% CI 0.39–0.58,  $p < 0.001$ ). Estimated 3-year OS was 86% versus 77%. The rate of grade 3–4 adverse events was 41% in the dabrafenib plus trametinib arm versus 14% with placebo; 26% of patients treated with targeted therapy had to discontinue because of TRAEs.

Another phase III double-blind trial, BRIM-8, randomized patients with radically-operated melanoma and BRAF V600 mutation to vemurafenib 960 mg twice daily or placebo for 12 months [20]. The study included enrollment in two cohorts: cohort 1 (stage IIC, IIIA, IIIB) included 364 patients and cohort 2 (stage IIIC) included 184 patients. There was no statistically significant difference in DFS in cohort 2 (HR 0.80, 95% CI 0.54–1.18) with a median of 23.1 months in the vemurafenib group and 15.4 months with placebo. In cohort 1, median DFS was not achieved in the vemurafenib group, and was 36.9 months in the placebo group.

Grade 3/4 adverse events were reported in 57% with vemurafenib versus 15% with placebo across both cohorts.

### **34.4.2 Treatment of Metastatic Disease**

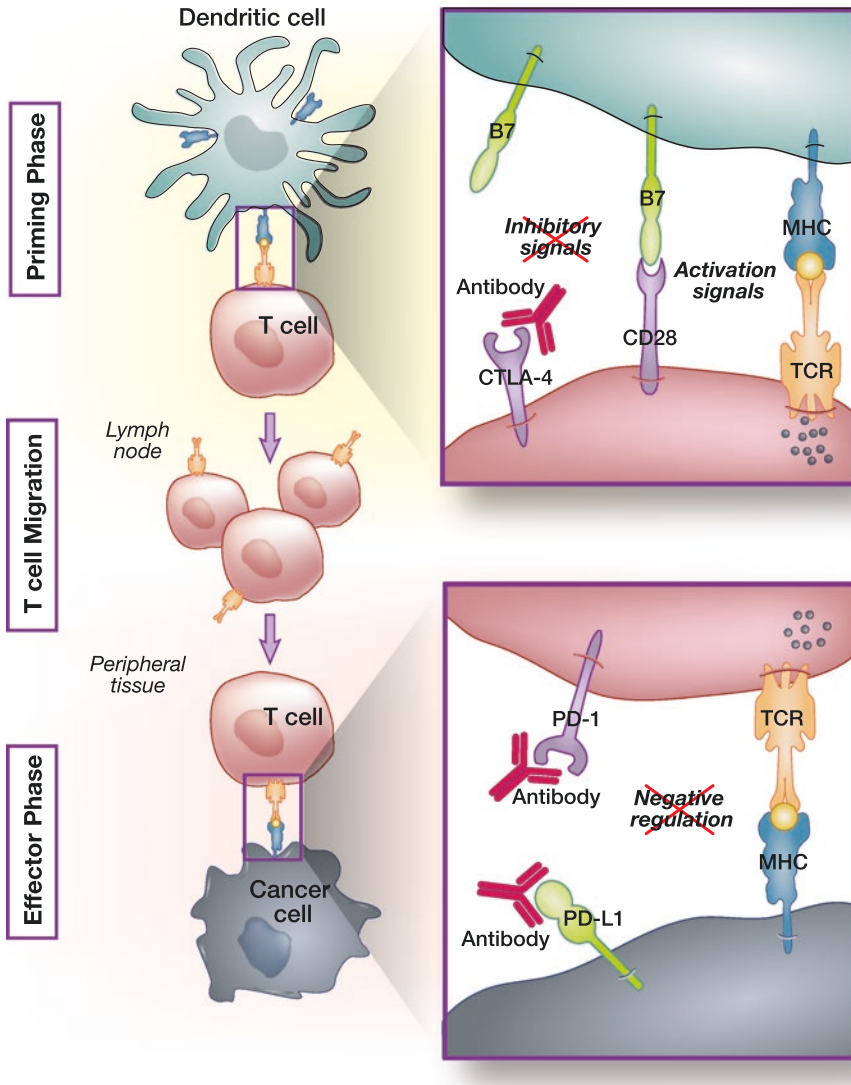
Until recently, chemotherapy of non-operable metastatic melanoma was considered almost exclusively palliative. However, since 2011, the emergence of new immunomodulating and molecularly targeted drugs has made significant improvements in survival a clinical reality.

#### **34.4.2.1 Immunotherapy**

Intravenous high-dose interleukin-2 induces an objective response rate (ORR) of 16% in selected patients with 6–7% complete responses [21]. Follow-up data indicate that about half of these complete responses are long-lasting, with some patients disease-free after 15 years. However, the risk of toxicity (capillary hyperpermeability syndrome with consequent risk of pulmonary edema, renal insufficiency, hypotension and cardiac dysfunction) means that this approach is not approved in Europe, although it is in the US.

In recent years, the introduction of checkpoint inhibitors has been a major turning point in melanoma immunotherapy (Fig. 34.2). The first drug to become available was ipilimumab, which is indicated for the treatment of patients with advanced melanoma at a dose of 3 mg/kg every 3 weeks for 4 cycles. Approval of ipilimumab was based on a three-arm phase III study in which 676 pretreated patients received ipilimumab with a peptide vaccine (gp100) or placebo, or gp100 plus placebo [22]. OS was significantly longer with ipilimumab alone or in combination with the vaccine compared with vaccine alone (10.1 versus 6.4 months). Ipilimumab was, however, associated with the risk of immune-related side effects which occurred in 60% of patients. Approximately 15% experienced grade 3–4 adverse events. Dermatitis was the most frequent immune-related event and diarrhea the most dangerous (perforation risk if not promptly treated). Immune-related toxicity can be fatal if left untreated, with seven deaths recorded in the phase III study. Severe cases should be promptly treated with high-dose corticosteroids.

In a second phase III study in 502 patients with previously untreated metastatic melanoma, patients were randomized to receive dacarbazine plus ipilimumab 10 mg/kg every 3 weeks for 4 cycles (induction phase) and then every 3 months until progression (maintenance phase) or dacarbazine plus placebo [23]. The ipilimumab arm demonstrated better OS compared to dacarbazine alone (11.2 vs 9.1 months). Three-year survival was 20.8% versus 12.2% (HR = 0.72;  $p < 0.001$ ). The incidence of grade 3–4 adverse events was 56% in the ipilimumab arm; in par-



**Fig. 34.2** Mechanisms of action of checkpoint inhibitors

The binding of CTLA4 with its ligand B7 (CD86), generates a negative signal that induces an anergy state in the T lymphocytes. The binding of ipilimumab to CTLA-4, preventing the initiation of the inhibitory signals, results in an increase in anti-tumor lymphocyte T activity. PD-1 is engaged by ligands PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273), which are expressed by tumor cells and infiltrating immune cells. Inhibition of the interaction between PD-1 and PD-L1 by immune checkpoint blockade, enhance anti-tumor responses, delay tumor growth, and facilitate tumor cell destruction.

ticular, there was evidence of increased liver toxicity. Despite the higher incidence of grade 3–4 adverse events, no toxicity-related deaths were recorded, evidencing the effectiveness of algorithms for the treatment of immune-related toxicity. Another randomized phase III study compared four doses of ipilimumab 3 mg/kg versus ipilimumab 10 mg/kg in 727 patients with advanced melanoma. The higher-dose treatment showed an advantage in terms of median OS (15.7 versus 11.5 months, HR 0.84;  $p = 0.04$ ) but with a higher incidence of immune-mediated toxicity, in particular diarrhea, colitis, hepatitis and hypophysitis [24].

More recently, PD-1 antibodies (nivolumab and pembrolizumab) have been shown to have superior efficacy and tolerability compared with ipilimumab. In a phase III study of first-line nivolumab versus dacarbazine in 418 patients with advanced wild-type BRAF melanoma, nivolumab provided superior OS, with 72.9% of patients in the nivolumab arm and 42.1% in the chemotherapy arm alive at 1-year [25]. Treatment with nivolumab also showed higher PFS. The incidence of grade 3–4 adverse events was lower in the nivolumab arm (11.7% versus 17.6%). A study update reported a 2-year OS of 57.7% with nivolumab versus 26.7% with dacarbazine [26].

A further phase III study evaluated the combination of nivolumab plus ipilimumab versus nivolumab alone versus ipilimumab alone as first-line treatment of 945 patients with advanced melanoma [27, 28]. Treatment with nivolumab alone provided superior PFS (HR 0.55, 95% CI 0.45–0.66) and OS (HR 0.65, 95% CI 0.53–0.80) compared with ipilimumab. The median PFS in the nivolumab group was 6.9 months versus 2.9 months in the ipilimumab group. Three-year OS was 52% with nivolumab and 34% with ipilimumab. ORR was also superior with nivolumab versus ipilimumab (44% versus 19%). Nivolumab had a better tolerability profile with 7.7% versus 14.8% of ipilimumab-treated patients discontinuing therapy.

Nivolumab was compared with investigator's choice chemotherapy (dacarbazine or paclitaxel with carboplatin) in 405 patients with advanced melanoma progressed after treatment with ipilimumab and, if BRAF-mutated a BRAF inhibitor [29]. At a median follow-up of 8.4 months, treatment with nivolumab was superior in terms of ORR (31.7% versus 10.6%). The rate of grade 3–4 adverse events was 9% in the nivolumab arm and 31% in the chemotherapy arm. PFS and OS data are not yet mature.

Pembrolizumab 10 mg/kg every 2 or 3 weeks up to progression (or maximum 2 years) was compared with ipilimumab in 834 patients with advanced melanoma who had not received more than one prior treatment-line [30]. Treatment with pembrolizumab had superior PFS to ipilimumab (every 2 weeks HR 0.58, 95% CI 0.46–0.72, every 3 weeks HR 0.58, 95% CI 0.47–0.72). Treatment with pembrolizumab was also superior in terms of 1-year OS (74.1%, 68.4% and 58.2% in the pembrolizumab every 2 weeks, pembrolizumab every 3 weeks and ipilimumab arms, respectively). In a study update, 33-month OS rate was 50% in the two pooled pembrolizumab arms and 39% with ipilimumab, with an ORR of 42% and 16% [31]. In addition, of the 104 patients who had completed pembrolizumab treatment (maximum of 2 years), 98% were alive at a median follow-up of 9 months after the end of treatment. PFS at 9.7 months was 91%. Ipilimumab had a higher incidence

of grade 3–5 adverse events (19.9%) compared with the two pembrolizumab arms (10.1–13.1%) and the rate of discontinuation due to TRAEs was higher with ipilimumab (9.4% versus 4.0–6.9%).

The efficacy of pembrolizumab was also evaluated in a phase II trial in 540 patients with pretreated advanced melanoma [32]. Six-month PFS was 34% with pembrolizumab 2 mg/kg every 3 weeks, 38% with pembrolizumab 10 mg/kg every 3 weeks and 16% with chemotherapy. An interim analysis demonstrated an improvement in PFS with pembrolizumab 2 mg and 10 mg versus chemotherapy (HR 0.57, 95% CI 0.45–0.73 and HR 0.50, 95% CI 0.39–0.64). Forty-eight percent of patients receiving chemotherapy crossed-over to pembrolizumab. Incidence of grade 3–4 adverse events was higher in patients treated with chemotherapy (26% versus 11–14%).

Anti PD-1 drugs (pembrolizumab and nivolumab) have an acceptable tolerability profile and lower toxicity than ipilimumab. In general, most adverse events are immune-mediated, so can be managed with symptomatic or immunomodulatory therapy (e.g. steroids), depending on the grade and duration of the event. The rate of treatment interruption with anti PD-1 due to toxicity is low (3–8% in clinical trials).

The combination of nivolumab plus ipilimumab or nivolumab monotherapy were compared with ipilimumab monotherapy in 945 patients with unresectable advanced melanoma [27, 28]. At 36 months follow-up, the combination treatment had superior PFS (HR 0.43, 95% CI 0.35–0.52), OS (HR 0.55, 95% CI 0.45–0.69) and ORR (58% versus 19%) compared with ipilimumab. Nivolumab alone was also superior to ipilimumab in terms of PFS, OS and ORR. Median PFS was 11.5 months for the combination, 6.9 months for nivolumab and 2.9 months for ipilimumab. Patients with positive PD-L1 tumor expression had similar 2-year OS with the combination and nivolumab monotherapy. Grade 3–4 toxicity was 59% in the combination arm, 21% in the nivolumab arm and 28% in the ipilimumab arm; there was a greater incidence of treatment discontinuation for toxicity in the combination arm (38.5%). At 3 years, survival rates were 58% with the combination, 52% with nivolumab and 34% with ipilimumab. After progression, 40% of patients in ipilimumab arm received anti PD-1.

In a phase II study of 142 patients, ORR was 59% with nivolumab plus ipilimumab in combination and 11% with ipilimumab alone [33, 34]. At a median follow-up of 24.5 months, OS was 64% in the combination arm and 54% in the ipilimumab arm (HR 0.74 95% CI 0.43–1.26). Two-year PFS was 51.3% for the combination and 12% for ipilimumab (HR 0.36, 95% CI 0.22–0.56). Grade 3–4 toxicity was observed in 54% of patients in the combination and 20% in the ipilimumab arm. No relevant differences were observed between BRAF wild-type or V600 mutated patients. Longer-term OS data for the combination are provided by a phase I study with a 68% 3-year OS, although this is based on only 53 patients [35, 36].

Currently the combination of nivolumab and ipilimumab has been approved by the US Food and Drug Administration and has received the positive opinion of the European Medicines Agency but is not available in all European countries.

### 34.4.2.2 Targeted Therapy

The phase III COMBI-d trial evaluated dabrafenib plus trametinib versus single-agent dabrafenib as first-line treatment in 423 patients with unresectable stage IIIC-IV BRAF V600 E/K mutated melanoma [37]. Combination treatment had superior PFS (HR 0.67, 95% CI 0.53–0.84), OS (HR 0.7, 95% CI 0.55–0.92) and ORR (69% versus 53%). Three-year OS was 44% in the combination arm compared with 32% in the monotherapy arm [38]. In the COMBI-v phase III study in 704 patients with unresectable stage IIIC-IV BRAF V600 E/K mutated melanoma, treatment with dabrafenib plus trametinib had superior OS (HR 0.69, 95% CI 0.53–0.89), PFS (HR 0.56, 95% CI 0.46–0.69) and ORR (64 versus 51%) compared with vemurafenib monotherapy [39].

In a pooled analysis of the COMBI-d and COMBI-V studies, patients with normal lactate dehydrogenase (LDH) and < 3 metastatic sites had the best outcomes with PFS and OS at 2 years of 46% (95% CI 40–54%) and 75% (95% CI 70–81%), respectively [40]. Conversely, patients with LDH  $\geq 2$  x upper normal limit (UNL) had the worst prognosis with PFS 8% (95% CI 3–19) and OS 40% (95% CI 29–55%) at 2 years. A 3-year update showed that baseline LDH, the number of metastatic sites and tumor burden can help identify patients treated with dabrafenib and trametinib with different prognosis [41].

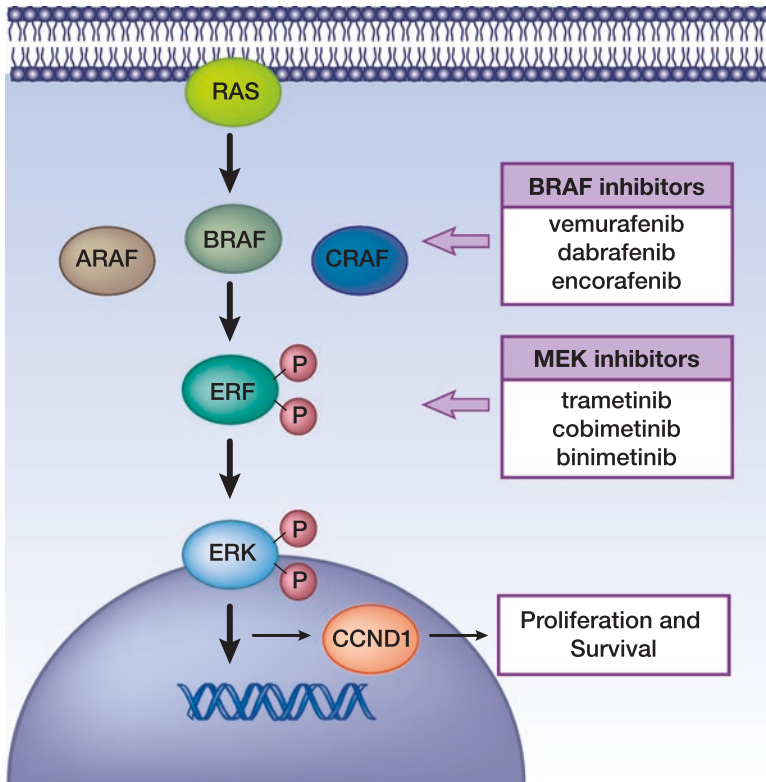
The CO-BRIM study evaluated vemurafenib plus cobimetinib versus single-agent vemurafenib as first-line treatment in 495 patients with unresectable stage IIIC-IV BRAF mutated melanoma [42, 43]. Combination treatment demonstrated a superior PFS (HR 0.51, 95% CI 0.45–0.79), OS (HR 0.70, 95% CI 0.55–0.90, median 17.4 versus 22.3 months) and ORR (45% versus 68%). Compared to the COMBI-d/v studies, CO-BRIM included more patients with elevated LDH and therefore a more unfavorable prognosis.

The combination of a BRAF plus MEK inhibitor has a good tolerability profile, with a general reduction in the cutaneous adverse events typical of BRAF inhibitors (e.g. hyperproliferative lesions) (Fig. 34.3). However, there is a modest increase in the risk of ocular toxicity, diarrhea and hypertension. In addition, treatment with dabrafenib plus trametinib is associated with an increased risk of pyrexia, whereas treatment with vemurafenib plus cobimetinib has higher photosensitivity and increased transaminases.

In NRAS mutated melanoma patients, the phase III NEMO study compared the MEK inhibitor binimetinib with dacarbazine in 242 patients not pretreated or progressed on immunotherapy [44]. Patients treated with binimetinib had a higher PFS than dacarbazine (median 2.8 versus 1.5 months, HR 0.62, 95% CI 0.47–0.80). The benefit was greater in patients pretreated with immunotherapy (median PFS 5.5 versus 1.6 months). OS was not significantly different between groups. ORR was 15% with binimetinib and 7% with dacarbazine.

In melanomas with c-KIT mutations, treatment with the c-KIT inhibitors imatinib and nilotinib may be an option [45, 46]. However, these drugs are not registered for the treatment of melanoma.

In clinical practice, the choice of treatment depends on the extent of the disease, the need for a rapid response, the potential for long lasting responses, co-morbidities,



**Fig. 34.3** Rationale for the combination of BRAF and MEK inhibitors

Most common mechanism of acquired resistance to BRAF-inhibitors is MAPK reactivation through MEK. MEK + BRAF inhibition prevents the development of acquired resistance in pre-clinical models and the combined inhibition improve response rates, Overall Survival and PFS in BRAF mutated melanoma patients versus BRAF inhibitor monotherapy, with reduced incidence of cutaneous hyperproliferative toxicity by blocking paradoxical activation of the MAPK pathway from RAF inhibition

and patient preferences. Evaluation of the disease must also take into account the type of responses observed during immunotherapy compared to targeted therapy and/or chemotherapy. The use of immunomodulatory antibodies, in particular ipilimumab, has shown that unconventional responses can be observed, characterized by an initial increase in tumor burden or the appearance of lesions, with subsequent late and lasting response. This has prompted the formulation of specific response criteria for immunotherapeutic agents [47]. These criteria for response assessment, mainly developed in studies with ipilimumab, could also be applied to treatments with anti PD-1, even if unconventional responses are less frequent and studies of these drugs have mostly used the classic RECIST criteria. If pseudo-progression is suspected at the first evaluation of the disease, progression should be confirmed after approximately 4 weeks.



## 34.5 Future Developments

Novel combinations are being explored to identify regimens that can overcome primary or acquired resistance to anti-PD-1/PD-L1 and/or reduce toxicity compared to combination therapy with anti-CTLA-4 and anti-PD-1. These include the indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor, epacadostat in combination with an anti-PD-1 agent. Epacadostat with pembrolizumab or nivolumab has shown promising results with good tolerability in different solid tumors, including advanced melanoma [48, 49].

Another potential new treatment, entinostat, a selective histone deacetylase inhibitor has shown promising activity in combination with pembrolizumab in melanoma patients (n = 13) refractory to previous treatment with checkpoint inhibitors [50]. However, 62% of patients reporting treatment-related grade 3–4 adverse events.

The addition of the anti-lymphocyte activation gene-3 (anti-LAG-3) agent BMS-986016 to nivolumab showed encouraging initial efficacy and a similar safety profile to nivolumab monotherapy in patients with advanced melanoma who previously progressed on or after anti-PD-1/PD-L1 therapy [51]. ORR was 13%, with a 20% response rate in patients with LAG-3 expression  $\geq 1\%$  versus only 7% in LAG-3-negative (<1%) patients. Expression of PD-L1 had no impact on response. The safety profile was comparable to that of nivolumab monotherapy. If the role of LAG-3 as a predictive biomarker is confirmed, this type of combination may have advantages over ipilimumab plus nivolumab or other combination regimens, allowing the personalization of immune-oncology according with the expression of different biomarkers. Nivolumab has also been assessed in combination with the glucocorticoid-induced tumor necrosis factor receptor-related gene (GITR) agonist, BMS-986156 [52]. In a phase I/IIa study in patients with advanced solid tumors, BMS-986156 plus nivolumab showed antitumor activity with no dose-limiting toxicities.

Finally, there is an increasing interest in changing the tumor microenvironment to increase immune cell localization and activation to overcome resistance to anti-PD-1/PD-L1 therapies. These approaches include oncolytic viruses, such as Talimogene laherparepvec [53], and small molecules such as toll-like receptor agonists [54] and STING-agonists. Future studies are required to define the activity of these approaches in combination with immune checkpoint inhibitors in patients progressing on anti-PD-1/PD-L1 treatment.

### Key Points

- Molecular alterations associated with melanoma have been identified, especially in genes involved in the mitogen-activated protein kinase (MAPK) pathway responsible for regulating proliferation, invasion and cell survival processes.
- In general, about 50% of melanomas have mutations affecting the BRAF gene, mutations in the NRAS gene are observed in 15–20% of cutaneous melanomas and mutations of the c-KIT gene are observed in 1–3% of melanomas, with greater frequency in mucosal and acral melanomas (15–20%).

- A conservative surgical excision approach is favored with the extent based on the Breslow thickness.
- The search for the sentinel lymph node is fundamental for surgical staging with risk of lymph node involvement directly proportional to the Breslow thickness of the primary melanoma or the presence of mitosis.
- Complete lymph node dissection (CLND) is indicated for metastases to clinically evident regional lymph nodes.
- Interferon (IFN)- $\alpha$  has been, and in many countries is still, the only available adjuvant therapy for melanoma patients although immunomodulating antibodies and targeted therapies may provide new options.
- In recent years, the introduction of checkpoint inhibitors has been a major turning point in melanoma immunotherapy and has improved outcomes for patients with advanced melanoma.
- PD-1 antibodies (nivolumab and pembrolizumab) have been shown to have superior efficacy and tolerability compared with ipilimumab.
- Various combination regimens involving different immunotherapies, targeted therapies and other treatment modalities are being explored to help improve efficacy and tolerability.
- In clinical practice, the choice of treatment depends on the extent of the disease, the need for a rapid response, the potential for long lasting responses, comorbidities, and patient preferences. Evaluation of the disease must also take into account the type of responses observed during immunotherapy compared to targeted therapy and/or chemotherapy.

### **Clinical Case**

A 42-year old woman underwent excision of a pigmented atypical lesion of her back (July 2008). Pathological examination revealed nodular ulcerated melanoma, Breslow thickness 4.4 mm, stage pT4b. As recommended by NCCN guidelines, the patient underwent sentinel lymph node biopsy with wide excision a few weeks later, which was negative for relapsed/residual melanoma. She refused adjuvant IFN therapy. The patient was followed-up and remained negative for disease until December 2012. In February 2013, she was hospitalized in the Emergency Room due to a syncope, secondary to severe anemia (hemoglobin: 4.5 mg/dl). Ultrasonography revealed the presence of multiple liver metastases and an abdominal mass eroding the second portion of the duodenum. Her ECOG performance status was 1. In March 2013, a liver metastasis biopsy documented the presence of a metastatic melanoma with a BRAF V600E mutation detected. Her LDH level was higher than the upper normal limit. In April 2013, treatment with vemurafenib plus cobimetinib was started. Treatment was well tolerated and no dose reductions were needed. The patient experienced grade 2 cutaneous toxicity and grade 2 CPK elevation. She achieved a major partial response (reduction of >75% of disease) and treatment was continued until July 2014 when a CT scan confirmed partial remission on some lesions but revealed progression of disease on other lesions. Thus, therapy was stopped and second-line treatment with nivolumab 3 mg/kg every 2 weeks was started. Treatment was well tolerated and no severe adverse events were reported.

Grade 1 pruritus and grade 1 hypothyroidism were the only side effects reported by the patient. A CT scan performed in October 2014 revealed complete remission of disease. In March 2018, treatment with nivolumab is still ongoing with no dose delays having been needed. A complete response and well as grade 1 pruritus and hypothyroidism are still ongoing.

### Multiple-Choice Questions

1. Approximately what proportion of melanomas have mutations affecting the BRAF gene?
  - (a) Less than 10%
  - (b) Approximately 25%
  - (c) **Approximately 50%**
  - (d) Approximately 75%
  - (e) Over 90%
2. When should mutations of the c-KIT gene be evaluated?
  - (a) In BRAF-mutant and NRAS wild-type melanoma
  - (b) In NRAS-mutant and BRAF wild-type melanoma
  - (c) In BRAF-mutant and NRAS-mutant melanoma
  - (d) **In BRAF wild-type and NRAS wild-type melanoma**
  - (e) None of the above
3. What is the risk of lymph node involvement in melanoma with a Breslow thickness  $\geq 4$  mm?
  - (a) 10%
  - (b) 20%
  - (c) 40%
  - (d) **60%**
  - (e) 80%
4. From what disease stage should IFN- $\alpha$  be considered as adjuvant therapy?
  - (a) Stage I
  - (b) All stage IIA
  - (c) **Stage IIA with poor prognostic factors**
  - (d) Stage IIIA
  - (e) Stage IIIC
5. Which of the following treatments have been assessed as adjuvant therapy for melanoma?
  - (a) Ipilimumab
  - (b) Nivolumab
  - (c) Dabrafenib plus trametinib
  - (d) Vemurafenib
  - (e) **All of the above**

6. What proportion of patients with stage III melanoma receiving adjuvant therapy with ipilimumab 10 mg/kg EORTC 18071 study had to discontinue due to treatment-related adverse events?
- (a) 12%
  - (b) 24%
  - (c) 36%
  - (d) **52%**
  - (e) 66%
7. What is the indicated dosage regimen for ipilimumab for the treatment of unresectable or metastatic melanoma?
- (a) 3 mg/kg every 2 weeks for 4 cycles
  - (b) **3 mg/kg every 3 weeks for 4 cycles**
  - (c) 3 mg/kg every 3 weeks for 8 cycles
  - (d) 10 mg/kg every 2 weeks for 4 cycles
  - (e) 10 mg/kg every 4 weeks for 4 cycles
8. What percentage of 676 pretreated patients treated with ipilimumab had immune-related side effects in a three-arm phase III study?
- (a) 20%
  - (b) b.30%
  - (c) 40%
  - (d) 50%
  - (e) **60%**
9. What did a randomized phase III study that compared four doses of ipilimumab 3 mg/kg versus ipilimumab 10 mg/kg in patients with advanced melanoma report?
- (a) No differences between doses
  - (b) Improved OS and reduced immune-related toxicity with the higher dose
  - (c) **Improved OS and increased immune-related toxicity with the higher doses**
  - (d) Worse OS and reduced immune-related toxicity with the higher dose
  - (e) Worse OS and increased immune-related toxicity with the higher doses
10. How did treatment with nivolumab compare with ipilimumab in a phase III study in 945 patients with advanced melanoma?
- (a) No significant differences
  - (b) Improved OS, improved PFS and increased immune-related toxicity
  - (c) **Improved OS, improved PFS and reduced immune-related toxicity**
  - (d) Worse OS, worse PFS and increased immune-related toxicity
  - (e) Worse OS, worse PFS and reduced immune-related toxicity

11. What is the rate of treatment interruption with anti PD-1s due to in clinical trials?
- (a) **3–8%**
  - (b) 10–12%
  - (c) 15–20%
  - (d) 35–30%
  - (e) >40%
12. Among patients treated with dabrafenib plus trametinib, which had the best prognosis based on LDH level and number of metastatic sites?
- (a) Elevated LDH and  $\geq 3$  metastatic sites
  - (b) Normal LDH and  $\geq 3$  metastatic sites
  - (c) Elevated LDH and  $< 3$  metastatic sites
  - (d) **Normal LDH and  $< 3$  metastatic sites**
  - (e) No differences between above groups
13. What is the effect on toxicity of combined BRAF plus MEK inhibitor versus BRAF inhibitors monotherapy?
- (a) Reduced cutaneous toxicity, ocular toxicity, diarrhea and hypertension
  - (b) **Reduced cutaneous toxicity and increased ocular toxicity, diarrhea and hypertension**
  - (c) Increased cutaneous toxicity, ocular toxicity, diarrhea and hypertension
  - (d) Increased cutaneous toxicity and reduced ocular toxicity, diarrhea and hypertension
  - (e) No differences in toxicity
14. Which of the following factors should help determine treatment choice in advanced melanoma?
- (a) Need for a rapid response
  - (b) Potential for long lasting responses
  - (c) Co-morbidities
  - (d) Patient preference
  - (e) **All of the above**
15. What is talimogene laherparepvec?
- (a) Indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor
  - (b) **Oncolytic virus**
  - (c) Glucocorticoid-induced tumor necrosis factor receptor-related gene (GITR) agonist
  - (d) toll-like receptor agonist
  - (e) STING-agonist

**Questions Relating to Clinical Case**

16. In cases of clinical diagnosis of cutaneous melanoma, which of the following is recommended:
- (a) A primary large excision
  - (b) **An excisional biopsy**
  - (c) An incisional biopsy of the lesion
  - (d) Only follow up
  - (e) Sentinel lymph node biopsy + wide excision
17. After the excision of a cutaneous melanoma with 1.1 Breslow thickness, which of the following is recommended:
- (a) **Sentinel lymph node biopsy + wide excision**
  - (b) Wide excision
  - (c) Follow up
  - (d) Sentinel lymphnode biopsy
  - (e) Adjuvant treatment
18. In cases of metastatic melanoma, the BRAF mutation must be detected:
- (a) Only in a metastasis
  - (b) Only in primary melanoma
  - (c) In blood sample
  - (d) **Preferably on a metastasis but if this is not possible, on available tumor tissue including primary lesion**
  - (e) Only in body fluids
19. Targeted therapy with BRAF + MEK inhibitors for metastatic melanoma should be reserved to:
- (a) **V600 BRAF-mutated patients**
  - (b) BRAF mutated and wild type patients
  - (c) BRAF wild type patients
  - (d) NRAS mutated patients
  - (e) None of the above
20. Treatment with anti PD-1 (nivolumab or pembrolizumab) for metastatic melanoma should be continued:
- (a) Until completion of 1 year of treatment
  - (b) Until completion of 2 years of treatment
  - (c) Until completion of 3 years of treatment
  - (d) **Until confirmed progression of disease or unacceptable toxicity by the patient**
  - (e) For 4 cycles

21. In cases of progression of disease after treatment with BRAF + MEK inhibitor and anti PD-1, a metastatic melanoma patient with BRAF mutation should be treated with:
- (a) Treatment within a clinical trial
  - (b) Chemotherapy
  - (c) Ipilimumab
  - (d) MEK inhibitor
  - (e) **a or c**

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# Chapter 35

## Soft Tissue Sarcomas



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**Abstract** Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors of mesenchymal origin, accounting for less than 1% of all adult malignancies and 15% of pediatric cancers. The most common subtypes in adults are liposarcoma (which corresponds to 20% of all STS), leiomyosarcoma and undifferentiated pleomorphic sarcoma. Based on the pattern of dissemination and the risk of distant metastases a different imaging approach may be indicated for each STS subtype as a staging workup. However, a contrast enhanced chest computed tomography is recommended for all moderate or high grade STS as a baseline imaging. Surgery is the main treatment of localized STS. It is recommended that the resection of the primary tumor includes a 2 cm margin envelope of normal tissue surrounding the lesion. The indications for radiotherapy include: high grade tumors, large (>5 cm) proximal grade 2 tumors, head and neck STS, large or high grade retroperitoneal sarcomas, local recurrences or positive margins after surgery. Adjuvant chemotherapy is still not a consensus, but there are some histologies that are better responders, like: synovial sarcoma, myxoid or pleomorphic liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma. Metastatic soft tissue sarcomas are basically treated with chemotherapy. However, as there is not any highly effective treatment for the metastatic disease, the prognostic factors for prolonged survival are more related to the tumor biology than to the treatment itself.

**Keywords** Soft tissue sarcomas · Liposarcomas · Leiomyosarcomas · Synovial sarcomas · Limb salvage · Radiotherapy · Chemotherapy · Metastasis

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## 35.1 Introduction

Sarcomas are a heterogeneous group of malignant tumors of mesenchymal origin, accounting for less than 1% of all adult malignancies and 15% of pediatric cancers [1–3]. They can be divided into 2 broad categories: soft tissue sarcomas and bone sarcomas. But with the expansion in the molecular biology, they may also be divided in simple karyotypes and highly complex karyotypes sarcomas. The simple karyotypes sarcomas have simple genetic alterations such as translocations in myxoid/round-cell liposarcoma and synovial sarcoma, APC or B-catenin mutations in desmoid tumors and KIT or PDGFRA mutations in gastrointestinal stromal tumors (GISTs) [4]. The highly complex karyotypes sarcomas include dedifferentiated and pleomorphic liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma and myxofibrosarcoma [4].

Although some tumors are grouped in a specific subtype, they may behave different according to the site that it arises. Retroperitoneal and intra-abdominal lesions have a much greater risk of local recurrence than extremity lesions even considering a stratification for the same subtype, which emphasizes the value of determining the aspects of biology of each tumor.

## 35.2 Epidemiology

According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the United States, the incidence of Soft Tissue Sarcomas is approximately 3.4 per 100,000 [5]. It's a rare disease, even though its true incidence is underestimated, as some visceral sarcomas are likely counted with their organ of origin rather than with soft tissue sarcomas.

It's slightly more common in males than in females by 1.4:1 and the median age at diagnosis is 59 [5]. More than 50 different histologic subtypes have been identified. The most common subtypes in adults are liposarcoma (which corresponds to 20% of all STS), leiomyosarcoma (14% of all STS), undifferentiated pleomorphic sarcoma (UPS) (14% of all STS), GIST (9% of all STS), synovial (5% of all STS) and myxofibrosarcoma (5% of all STS) [6]. But, among elderly patients, UPS is the most common subtype. Rhabdomyosarcoma is the most common subtype in children and adolescents and is more commonly found in the head and neck region rather than the extremities. Epithelioid sarcoma is the most common subtype in the hand.

The lower extremity, which is the most common affected site, accounts for 28% of all STS. Visceral STS account for 22%, retroperitoneal sarcomas for 16%, whereas trunk and another sites account for 10% and 12%, respectively [7].

Liposarcoma is the leading type of STS on the lower extremities and on the retroperitoneum. Undifferentiated pleomorphic sarcoma (UPS) is the most common type on the upper extremities and on the trunk. Visceral STS are in their great majority gastrointestinal stromal tumors (GIST) [6].

### 35.3 Clinical Evaluation

Soft tissue sarcomas are usually asymptomatic masses at the beginning. But as they grow, compressive symptoms may arise, specially in case of visceral or retroperitoneal sarcomas. STS located on the extremities or on the trunk are usually first recognized by a palpable mass.

Although the clinical history and physical examination are important in the initial evaluation, symptomatology and physical findings are often nonspecific with significant overlap among presentations of neoplastic and nonneoplastic causes [8].

### 35.4 Risk Factors/Etiology

Sarcomas are in their great majority sporadic and idiopathic. They almost always arise *de novo* and not from a preexisting benign lesion. However, there are some important factors that can increase the chances to develop a sarcoma. Some recognized risk factors are: genetic predisposition (Li-Fraumeni's syndrome, neurofibromatosis and hereditary retinoblastoma), exposition to radiotherapy (RT), some chemotherapy regimens (cyclophosphamide, chlorambucil, melphalan, procarbazine and nitrosureas), infection (Kaposi's sarcoma is strongly associated with HIV and HHV8 infection), chronic lymphedema (called Stewart-Treves syndrome when associated to angiosarcoma), familial adenomatous polyposis (a major risk factor for desmoid tumors), ionizing radiation.

Ionizing radiation is a known factor that increases the risk of sarcoma development [9–12]. There is not a clear dose related to the development, but it is known that a STS may emerge within the radiation field of patients who received more than 50 Gy. They usually develop about 16 years after the RT, but this period may vary according to the histologic subtype.

The most common subtypes associated with a prior radiation are angiosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma and osteogenic sarcomas. They often develop at the edge of the radiation field and are mostly located on the chest wall or upper extremity mainly because they emerged in the area of an irradiated breast cancer and non-Hodgkin's lymphoma, which are the classic tumors associated with a further sarcoma development. Those tumors are often high-grade and have a poor prognosis.

### 35.5 Radiologic Assessment: Prior to the Biopsy

Diagnostic imaging plays a key role in the diagnosis and treatment. It's usually recommended that, prior to the biopsy, a radiologic evaluation is made to guide the physician to get a sample from an area with more representative material, avoiding

cystic and necrotic areas. It's also important that vascularized areas are not injured when performing the biopsy because of the risk of hematoma which can increase the volume of the lesion and change the therapeutic approach.

Several different diagnostic imaging examinations may be used in the initial evaluation of a suspected STS. The two most common modalities are the MRI (magnetic resonance imaging) and the CT (computed tomography) [13–18]. MRI provides greater soft tissue contrast than CT and therefore often allows for better definition of internal tumor soft tissue composition/intrinsic elements. MRI also provides better definition of adjacent structures, like vessels and nerves, which is of great importance for the planning of the surgery. CT better demonstrates tumor mineralization and better depicts cortical bone involvement, whereas MRI better demonstrates medullary edema [19].

## 35.6 Biopsy

Biopsy is essential for the diagnosis of a sarcoma. It may be obtained through open incisional or core needle. Core needle biopsy is the gold standard. However, if definitive diagnosis may require flow cytometry, cytogenetics, or molecular analysis for chromosomal translocations, a larger sample may be necessary and an incisional biopsy may be preferred. In cases where core needle biopsy is unsuccessful, an incisional biopsy is usually considered [20]. It's recommended that it is performed by an experienced surgeon, preferably by the same one who is going to operate. As the biopsy site needs to come out with the tumor, a badly planned biopsy may compromise the surgical outcome, once complications like hematomas or a biopsy which is out of a planned incision would impel a difficult excision.

Core needle is the preferred method because of its low incidence of complications and high diagnostic accuracy [21–24]. Although fine needle aspiration is not recommended for an initial approach of a suspicious lesion, it may be useful in confirming recurrences.

## 35.7 Staging

The American Joint Committee On Cancer (AJCC) 8th edition brought great changes into the staging for soft tissue sarcoma. There is now a different staging according to the anatomic site. An important change came with the exclusion of the depth criterion, so there is not a division by the fascia anymore (Table 35.1). Another important change was the reclassification of N1 disease into stage IV for primary sites in the extremity and trunk. For STS arising in the retroperitoneum, nodal metastases are still classified as stage III disease. As there is now a different staging for each anatomic site, a prognostic stage grouping need to be implemented for each location. Head and neck sarcomas got a new classification and needs data collection

**Table 35.1** American Joint Committee On Cancer (AJCC): Definitions for T, N, M (8th edition, 2017)

	Extremity, trunk and retroperitoneum	Abdomen and thoracic visceral organs	Head and Neck
Tx	Primary cannot be assessed		
T0	No evidence for primary tumor		
T1	< 5 cm	Organ confined	< 2 cm
T2	5–10 cm	Extension into tissue beyond organ a: Invades serosa or visceral peritoneum b: Extension beyond serosa (mesentery)	2–4 cm
T3	10–15 cm	Invades another organ	> 4 cm
T4	> 15 cm	Multifocal involvement a (2 sites); b (3–5 sites); c (> 5 sites)	a: orbital invasion, skull base/dural invasion, invasion of central compartment viscera, facial skeleton or pterygoid muscles b: brain parenchymal invasion, carotid artery encasement, prevertebral muscle invasion or central nervous system involvement via perineural spread.
N	N0: No lymph node involvement or unknown status		
	N1: Lymph node involvement		
M	M0: No metastasis		
	M1: Metastases present		

before defining a stage grouping. For abdominal and thoracic visceral sarcomas there is still no recommended prognostic stage grouping. For extremity, trunk and retroperitoneal sarcomas, the staging is shown in Table 35.2.

### 35.8 Staging Workup

The most common pattern of spread of the STS is hematogenous. A retrospective series reported that the proportion of lung/liver as a site of distant spread from a primary extremity sarcoma is 75:1, in contrast to primary retroperitoneal sarcoma, in which the ratio is 1:1.5, and visceral sarcomas in which the ratio is 1:10 [25].

Lymphatic spread is rare in sarcomas. However, certain subtypes, such as: synovial sarcoma, rhabdomyosarcoma, clear cell sarcoma, epithelioid sarcoma and the vascular sarcomas have a higher risk of nodal metastases. Bone metastases are more often detected in myxoid/round cell liposarcoma.

**Table 35.2** AJCC: Anatomic stage/prognostic groups (8th edition, 2017)

Stage	T	N	M	Grade
IA	T1	N0	M0	G1, GX
IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
II	T1	N0	M0	G2, G3
IIIA	T2	N0	M0	G2, G3
IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
	Any T	<b>N1</b> (for retroperitoneal sarcomas, N1 disease means stage III)	M0	Any G
IV	Any T	Any N	M1	Any G
	Any T	<b>N1</b> (for extremity or trunk sarcomas, N1 disease means stage IV)	M0	Any G

**Table 35.3** Additional imaging that need to be done at some specific subtypes of STS, besides the chest CT and the local imaging evaluation

Imaging approach	Subtype of STS
Abdominal/pelvic CT	Myxoid/round cell liposarcoma
	Epithelioid sarcoma
	Angiosarcoma
	Leiomyosarcoma
MRI of total spine	Myxoid/round cell liposarcoma
Central Nervous System MRI or CT	Alveolar soft part sarcoma
	Angiosarcoma

Thus, based on the pattern of dissemination and the risk of distant metastases a different imaging approach may be indicated for each STS subtype, although a contrast enhanced chest computed tomography (CT) is recommended for all moderate or high grade STS as a baseline imaging.

Myxoid/round cell liposarcoma, for example, has a totally different pattern of dissemination than well differentiated or pleomorphic liposarcomas. While those other liposarcomas often metastasize to the lungs, the myxoid/round cell subtype has a predilection for bones, specially hematopoietic bones, which justifies the need for an MRI of total spine (which has shown to be superior to bone scintigraphy or even PET-CT for depicting its bone metastases) and for fatty sites like the mediastinum, justifying the chest CT (lung metastases may also occur but are not so common as in other subtypes like the well differentiated/dedifferentiated or the pleomorphic liposarcomas) and the abdominal/pelvic CT (to rule out a retroperitoneal/abdominal involvement) [26].

In Table 35.3 below is shown the different imaging evaluations that need to be done at some specific subtypes of STS, besides the chest CT and the local imaging evaluation.

## 35.9 Surgery

Surgery is the main treatment of localized STS. It is recommended that the resection of the primary tumor includes a 2 cm margin envelope of normal tissue surrounding the lesion [27]. However, the exact width of the negative margin necessary for an optimal local control is hard to know, because of the retraction of the tissues when removed.

The biopsy site needs to be excised en bloc with the surgical specimen. Care must be taken not to violate the tumor, which is associated with a higher local failure rate even if radiation therapy is used [28]. If closed suction drainage is necessary, the drains should exit the skin close to the edge of the surgical incision, because an eventual re-resection or radiotherapy (RT) of that area may be necessary. Surgical clips should be placed to mark the periphery of the surgical field and other relevant structures to help guide potential RT, especially if resections with microscopically positive or grossly positive margins are anticipated.

It is also recommended that the fascia is resected, even for superficial lesions. But as it confers an adequate barrier against dissemination, thinner (1 to 2 mm) margins of fascia are likely adequate. The periosteum can also be used as a margin and so in the absence of frank bone invasion, resection up to and possibly including the periosteum (without further damage to the cortical bone) may be acceptable [29]. Resection of the periosteum should be limited to tumors abutting it. It is known that periosteal stripping may increase the risk of a later radiation-related pathologic fracture, but it may be done in order to achieve negative margins, once a margin free surgery is the main goal of the treatment [30–32].

The perineurium may also be used as margin when resecting a STS. The tumor can be resected away from a neurovascular bundle with the perineurium as margin. If an artery is involved, arterial reconstruction may be done, preferably using venous grafts, which had a significantly higher patency rate than reconstruction with artificial venous substitutes [33]. Although a venous reconstruction is not essential, it can be done in order to reduce the postoperative edema.

Some tumors associated with high rates of local recurrence, like myxofibrosarcoma and dermatofibrosarcoma need special care regarding the surgery. They both have microscopic components that extends beyond the visible tumor and so an extended margin may be necessary. But the myxofibrosarcoma is usually multifocal and have an infiltrative tail, which can be seen on MRI. The 2 cm margin for those lesions should be planned circumferentially around the tumor and these tails [34].

### 35.10 Lymphadenectomy

Nodal metastases are rare in STS and therapeutic lymphadenectomy is indicated only if clinically positive nodes are present or in sarcomas that emerged from a lymph node basin. But certain subtypes like rhabdomyosarcoma, angiosarcoma, clear cell sarcoma and epithelioid sarcomas have a higher rate of nodal involvement.



For those cases, sentinel lymph node biopsy is being studied, although, until now, its role remains unclear because prospective studies did not show any survival advantage and only a 5% to 7% rate of occult lymph node metastases with these high risk subtypes [35].

### 35.11 Limb Perfusion/Infusion

Patients who have advanced local disease with involvement of major neurovascular bundles or multifocality are candidates for isolated limb perfusion or infusion, which can provide higher doses of chemotherapy to the limb. Isolated limb perfusion with melphalan and tumor necrosis factor-alpha (TNF) is the recommended option based on recent studies. The Rotterdam group performed a study with 197 patients using melphalan plus TNF and achieved limb salvage rate of 87% with a perioperative mortality of 0.5% [36]. However, isolated limb perfusion with melphalan alone had limited success [37].

The limb perfusion normally uses hyperthermic solutions in a high flow rate and requires the dissection of the limb's major vessels. Isolated limb infusion is a less invasive alternative (with normothermic solutions in low flow rate) but a less effective technique, as showed in a phase 2 clinical trial, which included 32 patients using isolated limb infusion with melphalan plus dactinomycin and showed a 53% of significant response (25% had complete response and 28% a partial response) [38].

### 35.12 Surgical Management of Metastatic Disease

Although surgical metastasectomy for STS has been studied only in retrospective series, it offered longer median overall survival (OS) compared with historical controls [39–42]. But only medically fit patients with a controlled primary, limited and resectable metastatic disease are candidates for a metastasectomy [43].

For pulmonary metastases, there are two major prognostic factors: a margin-negative metastasectomy and a longer disease-free interval (DFI), preferably greater than 1 year, between resection of the primary and the metastases [44]. Others prognostic factors are number of metastatic pulmonary nodules (resection of more than 8 nodules being probably futile), tumor grade, tumor size (primary  $\leq 10$  cm is a positive prognostic factor) and patient age (older than 50 confers a worst prognosis) [44–47]. Histologic subtype is not defined as a prognostic factor, once many reports could not find a difference in OS between sarcoma subtypes [48–50]. However, a recent study with 155 patients with STS and pulmonary metastases found longer OS for leiomyosarcoma and shorter for liposarcoma or synovial sarcoma [51].

Despite aggressive surgical management, recurrence rates are still above 50% following the resection of pulmonary metastases [52]. However, some series have

shown improved OS with repeated resection of recurrent metastasis [50]. Regarding the operation, the pulmonary metastasectomy used to be mainly an open surgery, even because manual palpation identifies up to 25% more pulmonary metastases than CT [53]. But minimally invasive resections are not associated with shorter OS or greater recurrence compared with open surgery, even because it is mostly used for peripheral, low-volume metastatic disease [54].

Patients with synchronous pulmonary metastases do not benefit from metastasectomy and chemotherapy may be the initial treatment [55]. Only the ones who benefits from chemotherapy should be considered for surgery. Chemotherapy and radiotherapy may be used preoperatively or postoperatively, but they need to be discussed on a case-by-case basis.

Hepatic metastases are more common in visceral or retroperitoneal sarcomas, specially leiomyosarcomas [56]. Hepatic metastasectomy is still not a consensus and should be restricted to medically fit patients, with a long DFI and an oligometastatic disease [57, 58].

### 35.13 Radiotherapy

Amputation used to be the standard treatment for STS, but with the emergence of radiotherapy, the rate of amputation has been reduced to approximately 1% without any measurable fall in overall survival [59–64]. The indications for RT in STS include: high grade tumors, large (>5 cm) proximal grade 2 tumors, head and neck STS, large or high grade retroperitoneal sarcomas, local recurrences or positive margins after surgery. If available, brachytherapy should be considered for extremity STS and intraoperative RT followed by external RT for retroperitoneal sarcomas.

The optimal timing of RT is still motive of debate. The benefits of a preoperative radiation include delivery of a lower total dose (usually 50 Gy compared with 60–70 Gy after resection) to an oxygenated lesion in a smaller field (the postoperative field needs to cover the operative bed, surgical wound and drain sites) and besides that, it may reduce the seeding during surgical manipulation and thicken the pseudocapsule, easing the resection [65–67]. The postoperative radiation is favored if there is need for pathologic confirmation, concern for wound healing or radiation complications to delay definitive resection. The myxoid-round cell liposarcomas are particularly more sensitive to radiation than others STS histologies, including their metastatic lesions; which can be effectively palliated with RT.

In summary, preoperative RT is preferred for larger lesions specially involving critical structures and for extremities, since few acute wound healing complications occurred in upper extremity STS and the wound complications with lower extremity STS can usually be managed. Surgery is usually performed 3–6 weeks after the completion of radiation and care must be taken to examine the pathologic specimen for positive margins, which may necessitate consideration of a postoperative boost. In contrast, postoperative therapy (at least 60 Gy) is usually preferred after an unplanned excision or

unexpectedly difficult resection, failure to obtain negative margins, or possibly when wound closure is expected to be under greater tension.

Although adjuvant RT at higher doses can also improve outcomes in patients with positive margins, local control is still worse with positive as compared with negative margins and resection to negative margins is preferred if additional conservative surgery can be performed.

### 35.14 Chemotherapy: Adjuvant

Adjuvant chemotherapy is still not a consensus. However, two important meta-analyses showed benefit, especially for recurrence-free survival [68, 69]. The SMAC (Sarcoma Meta-Analysis Collaboration) study from 1997 showed a slight benefit in OS for the group of adjuvant chemotherapy but only for extremity and trunk STS [70]. Another meta-analysis, published in 2008 and which included 18 trials with 1953 patients, showed a statistically significant benefit in overall survival but only for the group that used doxorubicin plus ifosfamide (the doxorubicin alone group showed benefit as well but not statistically significant) [68].

However, the results of individual studies are controversial. Frustaci et al. [70] in 2001 brought a study with 104 patients comparing 5 cycles of epirubicin 120 mg/m<sup>2</sup> plus ifosfamide 9 g/m<sup>2</sup> versus observation and showed a gain in disease-free survival (48 months for the adjuvant therapy versus 16 months for the observation group) and OS (75 months for the adjuvant therapy versus 46 months for the observation group). However, the EORTC (European Organisation for Research and Treatment of Cancer) 62931 [71] study, which randomized 351 patients comparing 5 cycles of doxorubicin 75 mg/m<sup>2</sup> plus ifosfamide 5 g/m<sup>2</sup> every 3 weeks versus observation, showed no benefit in relapse-free survival or OS.

There are some histologies that are better responders to chemotherapy like: synovial sarcoma, myxoid or pleomorphic liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma. But the results of the studies comparing adjuvant chemotherapy for those chemosensitive histologies are also controversial [72–74]. In 2014, the EORTC and the Soft Tissue and Bone Sarcoma Group (STBSG) coordinated two large trials of adjuvant chemotherapy in localized high-grade STS. As both studies failed to demonstrate benefit in OS, they tried to identify subgroups of patients from those trials who could benefit from adjuvant chemotherapy. They concluded that adjuvant chemotherapy is not associated with better OS in any pathology subgroup and that adjuvant chemotherapy for STS remains an investigational procedure and is not a routine standard of care.

Considering all that have been published, adjuvant chemotherapy should be administered with doxorubicin plus ifosfamide in high dosages and may be considered for high risk patients (tumors greater than 5 cm in diameter, high grade and deep to the fascia) with chemosensitive histologies (specially myxoid-round cell liposarcoma and synovial sarcoma) but needs to be discussed on a case-by-case basis once its benefits are still not a consensus.

### 35.15 Chemotherapy: Neoadjuvant

There are no randomized trials comparing neoadjuvant chemotherapy (with no adjuvant chemotherapy) versus observation. The Italian and the Spanish Sarcoma Group developed an international multicentric randomized phase 3 clinical trial [75] with extremity and trunk STS that compared 3 preoperative cycles of epirubicin 120 mg/m<sup>2</sup> and ifosfamide 9 g/m<sup>2</sup> versus this same preoperative scheme plus two postoperative cycles. The non-inferiority of 3 cycles of a full-dose conventional chemotherapy in comparison to five was confirmed. A retrospective series [76] showed that neoadjuvant chemotherapy did not increase postoperative morbidity and could also be used to assess the tumor response to chemotherapy.

Another phase 3 clinical trial, the ISG-STG 1001, showed the superiority of the neoadjuvant administration of standard chemotherapy (epirubicin 120 mg/m<sup>2</sup> plus ifosfamide 9 g/m<sup>2</sup>) to a histotype-tailored regimen [77]. However, the benefit with the standard chemotherapy suggests that this might be the added value of neoadjuvant chemotherapy itself in patients with high-risk STS [77].

Since the neoadjuvant approach may reduce the tumor burden (which can be better evaluated by PET-CT [78]), it is basically indicated for large or unresectable tumors, especially for extremity STS in order to make a posterior attempt of a conservative surgery.

### 35.16 Management of Local Recurrences

For local recurrences, it is important to know what kind of treatment was used on the first approach. For patients with no prior radiation, conservative surgery associated with radiotherapy is recommended. The RT may be done pre-operatively or post-operatively and this decision must be individualized. For patients with prior radiation, conservative surgery with re-irradiation also needs to be discussed on a case-by-case basis. If re-irradiation is considered, a brachytherapy or intensity-modulated RT is usually the choice in order to reduce the risk of toxicity.

Although conservative surgery is the first surgical option for local recurrences, approximately 10–25% of patients with local recurrence will have involvement of a great neurovascular bundle or bone or even a great amount of soft tissue and skin, making a conservative surgery not viable [79–81]. For those cases, the same options used for a primary attempt of resection may be used and schemes of chemotherapy and/or RT pre-operatively should be considered, as well as limb perfusion/infusion techniques.

Special consideration needs to be made for low grade retroperitoneal liposarcoma recurrences and desmoid tumors recurrences (or even primaries as well), which can be followed symptomatically and if surgery is considered in unresectable cases, even an incomplete resection can provide prolongation in survival and successful symptom palliation.

### 35.17 Soft Tissue Sarcoma: Metastatic

Metastatic soft tissue sarcomas are basically treated with chemotherapy. However, as there is not any highly effective treatment for the metastatic disease, the prognostic factors for prolonged survival are more related to the tumor biology than to the treatment itself [82].

The standard chemotherapy regimen is based on anthracyclines as first-line treatment. Although the studies with anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and or dacarbazine) have shown controversial results regarding overall survival, they are also valid as first-line options for medically fit patients [83].

New drugs are being tested in randomized phase 2 studies, such as the olaratumab. The combination of olaratumab with doxorubicin in patients with advanced STS achieved a significant improvement of 11.8 months in OS; median OS was 26.5 months with olaratumab plus doxorubicin and 14.7 months with doxorubicin alone. Another drug that have been tested is the aldoxorubicin, a novel albumin-binding prodrug of doxorubicin. Aldoxorubicin improved progression-free survival and tumor response, but it did not show an increase in OS [84].

As second-line treatment, new drugs such as pazopanib, trabectedin, eribulin and gemcitabine are acceptable options. Pazopanib is a multi-targeted tyrosine kinase inhibitor which is active in patients with advanced non-adipocytic STS. The PALETTE study, a phase 3 trial, compared pazopanib 800 mg once daily with placebo in non-adipocytic STS [85]. The OS was 12.5 months with pazopanib versus 10.7 months with placebo. However, 3.3% of the patients in the PALETTE study and 14% of the patients of a more recently published case report [87] developed a difficult to treat pneumothorax. Trials with pazopanib in renal cell carcinoma, urothelial carcinoma and cervix carcinoma did not report pneumothorax, suggesting it is a specific adverse event in STS patients [86].

A phase 3 study compared eribulin plus dacarbazine versus dacarbazine alone in advanced liposarcoma and leiomyosarcoma patients [87]. It showed that the combination improved OS by 2 months (13.5 months for the combination versus 11.5 months for observation). Another phase 3 multicenter clinical trial involving liposarcomas and leiomyosarcomas studied trabectedin versus dacarbazine after a prior therapy with an anthracycline and at least one additional systemic regimen [88]. Although trabectedin did not improve OS over dacarbazine (12.4 months for trabectedin versus 12.9 months for dacarbazine), it showed superior disease control.

The study Alliance A091401 [89], a randomised phase 2 trial, investigated the efficacy of nivolumab plus ipilimumab versus nivolumab alone in metastatic STS with a primary endpoint of objective response. The nivolumab alone does not warrant further study due to its limited efficacy. But nivolumab combined with ipilimumab demonstrated promising efficacy in certain subtypes (alveolar sarcoma, leiomyosarcoma, UPS, myxofibrosarcoma and angiosarcoma).

**Questions**

1. Soft tissue sarcomas comprises a heterogeneous group of rare diseases. In most cases, there is no known etiologic factor. However, literature describes some well established risk factors. Which of the following statements about these risk factors is not true?
  - (a) Previous exposition to ionizing radiation is related to the risk of development of a subgroup of radiation-induced sarcomas that are diagnosed most often until 5 years after exposition.
  - (b) Viral infections may be related to some specific sarcoma subtypes (Kaposi's sarcoma).
  - (c) Some genetic predisposition syndromes are major risk factors, among them: Li-Fraumeni, neurofibromatosis and familial adenomatous polyposis (FAP) syndrome.
  - (d) Stewart-Treves syndrome consists of an angiosarcoma related to chronic lymphedema (idiopathic, infectious or postoperative).

Answer: (a)

- (a) Radiation-induced sarcomas are most often diagnosed after 16 years, although this period may vary depending on the subtype that will arise.
2. Soft tissue sarcomas are rare and comprises 1% of all malignancies in adults. They can affect virtually any anatomic site, occurring more frequently in some locations. About sarcomas, which of the following is not true?
    - (a) The retroperitoneum is one of the most common sites of origin, comprising 16% of the cases.
    - (b) The extremities are the most affected anatomic location, specially the upper extremity (arm and forearm).
    - (c) The visceral sites are commonly affected, GIST being the most common histologic subtype in this region.
    - (d) Sarcomas are malignant tumors of mesenchymal origin, with more than 50 histological subtypes. Liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma are the most common ones.

Answer (b)

- (b) The lower extremity, which is the most common affected site, accounts for 28% of all STS
3. About the radiation induced sarcomas, which of the following is correct?
    - (a) They often develop at the edge of the radiation field.
    - (b) They usually have a better prognosis.
    - (c) Angiosarcoma is the only subtype associated.
    - (d) They usually develop at the extremities.

Answer (a)

They often develop at the edge of the radiation field, suggesting incomplete repair of normal tissue.

They usually have a poorer prognosis.

Angiosarcoma, osteogenic sarcomas and UPS are the most common subtypes that are associated.

They are mostly located on the chest wall or upper extremity mainly because they emerged in the area of an irradiated breast cancer and non-Hodgkin's lymphoma, which are the classic tumors associated with a further sarcoma development.

4. A 60-year-old man presented with a slow growing, palpable mass in his right thigh, noted 3 years ago. During physical examination, you notice a deep, firm, immovable 9.0 cm tumor in the lateral aspect of the right thigh. What is the most appropriate next step for diagnosis?
  - (a) Enhanced contrast CT to study the nature, localization of the tumor and assess femur medullary involvement.
  - (b) Incisional biopsy under sedation.
  - (c) Fine-needle aspirate.
  - (d) MRI to study the tumor composition and relation to adjacent structures, which may allow a better planning of the biopsy and surgery.

Answer (d)

CT better demonstrates tumor mineralization and better depicts cortical bone involvement, whereas MRI better demonstrates medullary edema.

Core needle biopsy is now the gold standard, with the incisional biopsy reserved for when a bigger sample is needed.

Fine needle aspirate is most of the times not diagnostic for soft tissue sarcomas.

It's usually recommended that, prior to the biopsy, a radiologic evaluation is made so it can guide the physician to get a sample from an area with more representative material, avoiding cystic and necrotic areas. It's also important that vascularized areas are not injured when performing the biopsy because of the risk of hematoma which can increase the volume of the lesion and change the therapeutic approach.

5. About the soft tissue sarcomas, which of the following is correct?
  - (a) Desmoid tumors are high grade lesions that usually present with lung metastases
  - (b) Myxoid/round cell liposarcomas are chemosensitive and radiosensitive lesions
  - (c) Neoadjuvant chemotherapy with 3 cycles showed inferior results compared to a 5 cycles scheme combining 3 cycles pre-operatively and 2 cycles postoperatively.
  - (d) Nodal metastases for retroperitoneal sarcomas mean stage IV disease

Answer (b)

Desmoids are low grade lesions which does not metastasize.

An international multicentric randomized phase 3 clinical trial with extremity and trunk STS that compared 3 preoperative cycles of epirubicin 120 mg/m<sup>2</sup> and ifosfamide 9 g/m<sup>2</sup> versus this same preoperative scheme plus two postoperative

cycles. The non-inferiority of 3 cycles of a full-dose conventional chemotherapy in comparison to five was confirmed

Nodal metastases for extremity sarcomas mean stage IV disease, but for retroperitoneal sarcomas it means a stage III disease.

6. A 70-year-old man was diagnosed with an undifferentiated pleomorphic sarcoma (UPS) on the right arm. The complete imaging staging revealed synchronous pulmonary metastases. Which of the following is not true about the soft tissue sarcomas?
- (a) UPS is the most common sarcoma on the upper extremities
  - (b) UPS is the most common subtype among elderly patients
  - (c) The best treatment option would be the resection of the primary followed by pulmonary metastasectomy.
  - (d) The baseline imaging staging for UPS is composed of a chest CT and a MRI/CT of the primary site.

Answer (c)

Patients with synchronous pulmonary metastases do not benefit from metastasectomy; and chemotherapy may be the initial treatment.

7. A 45-year-old woman underwent resection of a 5 cm soft tissue mass from her back. Pathological report revealed an undifferentiated pleomorphic sarcoma, with positive margins. Staging workup was negative for metastasis. What is the most appropriate next step?
- (a) Observation
  - (b) Radiotherapy
  - (c) Doxorubicin based chemotherapy
  - (d) Reresection

Answer (d)

Although adjuvant radiation may be an option, the main goal of the treatment for most STS is a resection with negative margins.

8. Which of the following statements is not true about the staging of soft tissue sarcomas?
- (a) Unlike extremity localized tumors, retroperitoneal sarcomas with nodal metastasis are grouped in stage III
  - (b) The location in relation to the fascia (superficial or deep) remains an important staging criterion
  - (c) Head and neck sarcomas have a proper staging system, similar to other malignant head and neck tumors
  - (d) Histological grade remains a relevant factor in staging.

Answer (b)

The American Joint Committee on Cancer (AJCC) – 8th edition brought great changes into the staging for soft tissue sarcoma. There is now a different staging



according to the anatomic site. An important change came with the exclusion of the depth criterion, so there is not a division by the fascia anymore

9. A 63-years-old man presented with a fast-growing mass in his right axillary region. He sought medical attention and was submitted to adequate imaging workup and core needle biopsy. Pathology and staging revealed an 8.0 cm synovial sarcoma with no metastatic disease. He underwent wide resection and axillary lymphadenectomy. Pathological report demonstrated an 8.0 cm synovial sarcoma, resected with free margins and three lymph nodes harboring sarcoma metastasis. Which of the following depicts the most appropriate statement?
- There is no need for lymphadenectomy, since nodal metastases are rare in soft tissue sarcomas.
  - The patient should be referred to medical oncology, once nodal metastasis characterizes stage III disease
  - The patient should be referred to radiotherapy, to evaluate adjuvant treatment, and medical oncology to discuss, on a case-by-case basis, the benefit of adjuvant chemotherapy regimen in this high-risk patient
  - The treatment is complete and the patient should be followed every 6 months

Answer (c)

Synovial sarcoma is a high grade and a chemosensitive sarcoma subtype. As this is a high risk (> 5 cm, high grade sarcoma with nodal metastasis) patient, adjuvant chemotherapy may be indicated. The lymph node dissection showed 3 metastatic lymph nodes, making it reasonable to irradiate this area in order to try to achieve a better local control.

10. Nodal metastases in soft tissue sarcomas are a rare event. However, they exist, and may be associated with specific sarcoma subtypes. Which of the following contains the subtypes of greater risk for nodal dissemination?
- Synovial sarcoma, clear cell sarcoma and malignant nerve sheath tumor
  - Epithelioid sarcoma, lymphangiosarcoma and liposarcoma
  - Angiosarcoma, leiomyosarcoma and fibrosarcoma
  - Rhabdomyosarcoma, angiosarcoma and clear cell sarcoma

Answer (d)

Synovial sarcoma, rhabdomyosarcoma, clear cell sarcoma, epithelioid sarcoma and the vascular sarcomas have a higher risk of nodal metastases.

11. Which one of the following is the most common subtype of extremity soft tissue sarcomas?
- Undifferentiated pleomorphic sarcoma
  - Liposarcoma
  - Leiomyosarcoma
  - Myxofibrosarcoma

Answer (b)

Liposarcoma is the most common subtype in the extremities, particularly in the lower extremities.

12. Some soft tissue sarcomas metastases have a predilection for central nervous system. Which of the following alternatives contains one of these sarcoma subtypes?
- (a) Epithelioid sarcoma
  - (b) Desmoid tumors
  - (c) Leiomyosarcoma
  - (d) Alveolar soft part sarcoma

Answer (d)

Alveolar soft part sarcoma and angiosarcoma are the subtypes most commonly associated to central nervous system metastasis.

13. Myxoid/Round cell liposarcoma needs to be properly staged with a lot more than just a physical examination. Which of the following contains the complete baseline imaging approach for those tumors?
- (a) Chest CT only
  - (b) Chest and abdominal/pelvic CT
  - (c) Chest and abdominal/pelvic CT plus MRI of total spine
  - (d) Chest and abdominal/pelvic CT plus Central Nervous System MRI

Answer (c)

Myxoid/round cell liposarcoma has a totally different pattern of dissemination than well differentiated or pleomorphic liposarcomas. While those other liposarcomas often metastasize to the lungs, the myxoid/round cell subtype has a predilection for bones, specially hematopoietic bones, which justifies the need for an MRI of total spine (which has shown to be superior to bone scintigraphy or even PET-CT for depicting its bone metastases) and for fatty sites like the mediastinum, justifying the chest CT (lung metastases may also occur but are not so common as in other subtypes like the well differentiated/dedifferentiated or the pleomorphic liposarcomas) and the abdominal/pelvic CT (to rule out a retroperitoneal/abdominal involvement).

14. A 70- year-old female patient just had a 5 cm, high grade, undifferentiated pleomorphic sarcoma removed from her arm. The pathological report showed compromised microscopic margin. What is the most appropriate approach for this case?
- (a) Reresection to negative margins
  - (b) Adjuvant radiotherapy
  - (c) Adjuvant chemotherapy
  - (d) Observation and if it relapses, resection

Answer (a)

Although adjuvant radiotherapy or even adjuvant chemotherapy may be options, the main goal of the treatment of most high-grade sarcomas is to obtain negative margins whenever possible.

15. A 40-year-old male patient was diagnosed with a 5 cm myxoid/round cell liposarcoma in his right thigh, but distant to the neurovascular bundle. Physical examination revealed enlarged lymph nodes in the right groin, whose biopsy was positive for metastatic sarcoma. The complete imaging staging showed a metastatic disease only to the lymph nodes in right groin. Which of the following items contains the correct clinical stage and treatment?

- (a) Stage IV / Chemotherapy only
- (b) Stage III / Resection of the primary and lymphadenectomy
- (c) Stage IV / Neoadjuvant chemotherapy followed by resection of the primary with no lymphadenectomy
- (d) Stage IV / Resection of the primary and lymphadenectomy

Answer (d)

N1 for extremity sarcomas means a stage IV disease (for retroperitoneal sarcomas it means a stage III disease)

Although many options of treatment are available in this case, like neoadjuvant chemotherapy (myxoid/round cell liposarcoma is particularly a chemosensitive subtype); the resection of the primary to negative margins with lymphadenectomy (since no other distant disease is present) is the most important part of the treatment.

16. About soft tissue sarcomas, which of the following is not true?

- (a) Limb perfusion with melphalan alone showed to be non-inferior to limb perfusion with melphalan and TNF.
- (b) Isolated limb infusion is a less invasive alternative (with normothermic solutions in low flow rate) but a less effective technique, as showed in recent phase 2 clinical trials.
- (c) Epithelioid sarcoma is the most common subtype in the hand.
- (d) Rhabdomyosarcoma is the most common subtype in children and adolescents and are more commonly found in the head and neck region rather than the extremities.

Answer (a)

Isolated limb perfusion with melphalan and tumor necrosis factor- $\alpha$  (TNF) is the recommended option based on recent studies. The Rotterdam group performed a study with 197 patients using melphalan plus TNF and achieved limb salvage rate of 87% with a perioperative mortality of 0.5% (36). However, isolated limb perfusion with melphalan alone had limited success.

### Clinical Case

A 62-year-old female patient was referred to our service with an asymptomatic palpable mass on her right thigh. She brought an ultrasound that revealed a

hypoechoic mass with some internal debris and measuring 5.6 x 12 x 6.1 cm in the middle of the quadriceps muscle. After a complete physical examination which showed clinically positive lymphnodes in the right groin, a magnetic resonance of the right thigh was ordered, which showed a complex lesion with some areas of necrosis but with no neurovascular bundle or bone involvement. A core needle biopsy of the lesion was performed and revealed a pleomorphic liposarcoma. Fine needle aspiration of the lymphnodes in the groin was positive for neoplastic cells. A chest CT was ordered and did not show any metastatic implants.

1. Question: What would be your next step? What's the staging of this disease? Lymphadenectomy would be indicated in this case?

Answer:

1. The patient has a stage IV disease with isolated regional (ipsilateral groin) disease.
2. Lymphadenectomy is indicated. Therapeutic lymphadenectomy is indicated only if clinically positive nodes are present or in sarcomas that emerged from a lymph node basin.
3. Next step would be the resection of the primary with lymphadenectomy. As it is an undoubtedly resectable lesion (as shown in the MRI), we prefer an upfront surgery instead of using neoadjuvant approaches with chemotherapy or radiotherapy, although both neoadjuvant approaches are reasonable and may have been indicated. Neoadjuvant chemotherapy or radiotherapy is more frequently used when the primary is unresectable or resectable with adverse functional outcomes.

The patient was then treated with the resection of the primary to negative margins and with a right pelvic and inguinal lymphadenectomy. The pathological report confirmed a pleomorphic liposarcoma with 12cm in its greatest dimension. It also revealed 3 (out of 10) metastatic lymphnodes in the groin and 1 (out of 14) in the pelvis.

2. Question: What's your next step? Is radiotherapy/chemotherapy indicated?

Answer:

1. Radiotherapy is indicated. The indications for radiotherapy in STS include: high grade tumors, large (>5cm) proximal grade 2 tumors, head and neck STS, large or high grade retroperitoneal sarcomas, local recurrences or positive margins after surgery).
2. Chemotherapy is indicated. Adjuvant chemotherapy should be administered with doxorubicin plus ifosfamide in high dosages and may be considered for high risk patients (tumors greater than 5cm in diameter, high grade and deep to the fascia) with chemosensitive histologies (specially myxoid-round cell liposarcoma and synovial sarcoma) but needs to be discussed on a case-by-case basis once its benefits are still not a consensus. Although pleomorphic liposarcoma is not a chemosensitive histology, the patient had a large and high-grade primary with a stage IV disease.

Radiotherapy was then applied. Also, adjuvant chemotherapy was used with doxorubicin and ifosfamide in high dosages. The patient was followed and on the 6th month she presented at the office with a resectable local recurrence.

3. Question: What's your next step?

Answer:

1. New re-staging with a complete history and physical examination and a chest CT as baseline imaging staging.
2. If the new re-staging shows only the local recurrence, resection to negative margins is the most appropriate recommendation.
3. For patients with prior radiation, conservative surgery with re-irradiation needs to be discussed on a case-by-case basis. If re-irradiation is considered, a brachytherapy or intensity-modulated radiotherapy is usually the choice in order to reduce the risk of toxicity.

New re-staging was done and revealed a local recurrence only. So new resection to negative margins was performed. The patient is then being followed with a 3/3 months consultation.

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# Chapter 36

## Bone Sarcomas



**Gislaine Fernandes Silva, Daiane Pereira Guimarães, Hakaru Tadokoro, and Ramon Andrade De Mello**

**Abstract** Bone sarcomas are primary malignant tumors of osteoid producing cells adjacent to growth plates, which arise more frequently in long bones (Clark J, Rocques PJ, Crew AJ et al: *Nat Genet* 7:502–508, 1994). Unlike soft tissue sarcomas, which have a wide variety of histological subtypes, bone sarcomas have only three distinct categories: chondrosarcoma, Ewing’s sarcoma and osteosarcoma. Bone sarcomas are more common in children and young adults, with some exceptions in later years. The management of bone sarcomas varies considerably, according to histology, degree and stage (Devita H: *Rosemberg’s cancer: principles & practice of oncology*. In: VT DV Jr, Lawewnce TS, Rosemberg SA (eds) Chapter 121 with 404 contributing authors, 10th edn. LWW, New York, 2014).

**Keywords** Bone sarcoma · Chemotherapy · Radiotherapy

### 36.1 Introduction

Bone sarcomas are primary malignant tumors of osteoid producing cells adjacent to growth plates, which arise more frequently in long bones [1]. Unlike soft tissue sarcomas, which have a wide variety of histological subtypes, bone sarcomas have

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only three distinct categories: chondrosarcoma, Ewing's sarcoma and osteosarcoma. Bone sarcomas are more common in children and young adults, with some exceptions in later years. The management of bone sarcomas varies considerably, according to histology, degree and stage [2].

## 36.2 Incidence and Etiology

Bone sarcomas are rare tumors which incidence is <1 per 100.000 people living in the United States each year [3]. The specific incidence of chondrosarcoma is not well established, as low grade lesions are relatively common and there are no accurate records. About high-grade osteosarcoma and Ewing's sarcoma, the incidence is about one per million [2].

The etiology of bone sarcomas is not known [4]. Some conditions increase the risk of developing osteosarcoma, such as the TP53 gene mutation in Li-Fraumeni syndrome [5] and the RB1 gene mutation in patients with retinoblastoma [6].

Environmental factors are also related to the genesis of osteosarcomas, such as ionizing radiation which is responsible for approximately 3% of cases of bone sarcomas. In addition, treatment with alkylating agents is also known to increase the risk of osteosarcoma [4].

Some benign bone conditions predispose to the development of bone sarcoma, such as Paget's disease of bone [7], fibrous dysplasia, McCune-Albright syndrome and Mazabraud's syndrome [8]. Other benign tumors that can be pre-malignant include giant cell tumor, osteblastoma and synovial chondromatosis [9]. Even nononcological conditions such as chronic osteomyelitis and bone infarcts may progress to sarcomas [10].

## 36.3 Clinical Presentation

Patients typically present localized pain, some times that can last several months in duration. Other systemic symptoms, such fever, weight loss and malaise are usually not present. On physical examination, a soft tissues mass may be observed, which is often large and tender palpation. Osteosarcomas have a predilection for the metaphyseal region of the long bones. The most common sites of involvement are: distal femur, proximal tibia, proximal humerus, mid and proximal femur and other bones [11].

Laboratory evaluation is usually normal, except for elevations in alkaline phosphatase, lactate dehydrogenase, and erythrocyte sedimentation rate [12].

Between 10% and 20% of patients present macrometastatic disease at diagnosis. Distant metastases most commonly involve the lungs, but can also involve bone [13].

## 36.4 Diagnosis and Staging

The evaluation for diagnosis and staging should include an imaging examination of the bone involved. Magnetic resonance imaging (MRI) is preferred in most cases, since it has better definition of soft tissues, particularly neurovascular bundle, joint and marrow involvement [14].

Computer tomography (CT) scans are best suited to assess the presence of metastatic disease to the lung, however, they may underestimate the extent of lung involvement [15]. A PET or PET/CT quantifies the metabolic activity at the primary site and helps to exclude occult metastases. Its utility in the management of patients with osteosarcoma is well established and should be considered to be a standard of care [16].

Supreme caution must be taken regarding the way the biopsy is performed. Percutaneous fine needle or core procedures, especially when guided by imaging, such as ultrasonography, CT or MRI, can be successful in establishing a diagnosis. This method has the advantage maximizing sampling throughout the mass and minimizing contamination. The material obtained should be sufficient to perform all histological, immunohistochemical, cytometric and cytogenetic studies, allowing an accurate diagnosis, therefore, incisional biopsies are often performed, especially in pediatric cases. Excisional biopsy (resection) can be considered for smaller lesions that can be completely excised with negative margins and without functional impairment [17].

Staging should be performed according to the TNM (tumor, nodule, metastasis) guidelines with the principles established by the American Joint Committee on Cancer [18] (Table 36.1).

## 36.5 Treatment

### 36.5.1 *Chondrosarcoma*

Chondrosarcoma is a malignancy of the matrix producing cartilage with diverse morphological characteristics. Chondrosarcoma occurs most frequently between 40 and 70 years of age. When low grade (about 90% of chondrosarcomas), chondrosarcoma rarely metastasize, but can progress to high-grade, which has a higher metastatizing potential [19].

The surgical treatment offers the only chance of cure for all degrees and subtypes of localized chondrosarcoma. The type of surgery varies according to the histological grade, location and size of the tumor. For tumors with high or intermediate grades, local block excision is the treatment of choice [20]. Low-grade tumors can be treated with less extensive surgeries, intend to minimize the functional disability of these patients [21].

**Table 36.1** Bone sarcomas TNM staging AJCC UICC 2017

Primary tumor (T)	
Appendicular skeleton, trunk, skull, and facial bones	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor $\leq 8$ cm in greatest dimension
T2	Tumor $> 8$ cm in greatest dimension
T3	Discontinuous tumors in the primary bone site
Spine	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one vertebral segment or two adjacent vertebral segments
T2	Tumor confined to three adjacent vertebral segments
T3	Tumor confined to four or more adjacent vertebral segments, or any nonadjacent vertebral segments
T4	Extension into the spinal canal or great vessels
T4a	Extension into the spinal canal
T4b	Evidence of gross vascular invasion or tumor thrombus in the great vessels
Pelvis	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one pelvic segment with no extrasosseous extension
T1a	Tumor $\leq 8$ cm in greatest dimension
T1b	Tumor $> 8$ cm in greatest dimension
T2	Tumor confined to one pelvic segment with extrasosseous extension or two segments without extrasosseous extension
T2a	Tumor $\leq 8$ cm in greatest dimension
T2b	Tumor $> 8$ cm in greatest dimension
T3	Tumor spanning two pelvic segments with extrasosseous extension
T3a	Tumor $\leq 8$ cm in greatest dimension
T3b	Tumor $> 8$ cm in greatest dimension
T4	Tumor spanning three pelvic segments or crossing the sacroiliac joint
T4a	Tumor involves sacroiliac joint and extends medial to the sacral neuroforamen
T4b	Tumor encasement of external iliac vessels or presence of gross tumor thrombus in major pelvic vessels
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	

(continued)

**Table 36.1** (continued)

M category	M criteria			
M0	No distant metastasis			
M1	Distant metastasis			
M1a	Lung			
M1b	Bone or other distant sites			
Histologic grade (G)				
G	G definition			
GX	Grade cannot be assessed			
G1	Well differentiated, low grade			
G2	Moderately differentiated, high grade			
G3	Poorly differentiated, high grade			
Prognostic stage groups				
T	N	M	G	Stage group
T1	N0	M0	G1 or GX	IA
T2	N0	M0	G1 or GX	IB
T3	N0	M0	G1 or GX	IB
T1	N0	M0	G2 or G3	IIA
T2	N0	M0	G2 or G3	IIB
T3	N0	M0	G2 or G3	III
Any T	N0	M1a	Any G	IVA
Any T	N1	Any M	Any G	IVB
Any T	Any N	M1b	Any G	IVB

The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science + Business Media, LLC

As the cytotoxicity of radiotherapy is dependent on cell division and most chondrosarcomas have slow growth, these tumors are considered relatively, but not absolutely, radioresistant. Radiotherapy can be beneficial after an incomplete resection of a high-grade chondrosarcoma and in the palliative context, such as in situations where resection is not feasible or would cause an unacceptable morbidity [22].

Chondrosarcomas are considered chemoresistant tumors, and this characteristic can also be attributed to factors such as slow growth, drug resistance genes expression, difficulty of drugs accessing the tumor, because of large amount of extracellular matrix and poor vascularization and high activity of anti-apoptotic and pro-survival pathways [23, 24].

Although most patients with recurrent or metastatic chondrosarcoma do not respond to chemotherapies used for advanced sarcoma, there are isolated cases of successful treatment with ifosfamide alone, doxorubicin-based chemotherapy or single agent methotrexate. The highest benefit being observed in mesenchymal and dedifferentiated chondrosarcoma [25–27].

### 36.5.2 *Ewing's Sarcoma*

Ewing's sarcoma (ES) is a small, blue, round-cell tumor, periodic acid-Schiff positive, and CD99 positive. All ESs are high grade tumors. Molecular biology studies have shown that almost all of these tumors share a common rearrangement of genes involving the EWS gene on chromosome 22, and in most cases it is a recurrent chromosomal translocation, t(11;22)(q24;q12) [28].

ES is the third most common bone cancer. The incidence is higher in the second decade of life and young adults. The most common tumor sites correspond to the lower extremities (45%) followed by pelvic bones (20–25%) [29].

Despite the fact that fewer than 25% of patients have evident metastases at the time of diagnosis, ES is a systemic disease. Before routine chemotherapy use, almost all early diagnosed ES patients developed distant metastatic disease and eventually died. Chemotherapy can successfully eradicate occult metastases, and current treatment plans include chemotherapy, usually given before and after local treatment [30].

Current standard chemotherapy includes Vincristine, Doxorubicin and Cyclophosphamide (VDC) in alternating cycles with Ifosfamide and Etoposide (IE). Doxorubicin is replaced by Dactinomycin when it reaches the cumulative dose of 375 mg/m<sup>2</sup>. Cycles are repeated every 2 weeks, and are supported with granulocyte colony stimulating factor (300mcg/day) to facilitate recovery of the bone marrow. Four to six cycles of chemotherapy are given prior to local therapy and, after local treatment, additional cycles of the same treatment are given postoperatively for a total of 14–17 cycles [31].

The local treatment can be surgery, radiation or both. The choice depends on the patient's characteristics, potential damage and benefit (compensation between the functional outcome and the risk of a secondary radiation-induced malignancy) and patient's preference. There are no randomized trials comparing RT and surgery for local control, however, some retrospective series and a systematic review suggest superior local control with surgery [32].

Patients with metastatic disease at diagnosis often respond to the same type of systemic chemotherapy that is used for localized disease, but they present a significantly worse outcome than those with localized disease. The metastases site is an important variable, with better prognosis for patients with isolated lung and pleural metastases [33]. Unlike the experience for patients with localized disease, adding IE to VDC does not improve outcomes of patients with Ewing's Sarcoma of bone with metastases at diagnosis [34].

Patients with recurrent ES had few treatment options. These patients are candidates for clinical trials of new agents, and may be treated with some salvage chemotherapy regimens with activity documented in this setting. Many patients are treated with the same combination chemotherapy regimen used as part of initial therapy [35]. Other data suggest that a higher dose of ifosfamide may be active in patients with recurrent ES who were treated with lower doses of ifosfamide as part of the initial therapy [36]. Other combinations of active agents are Gemcitabine and Docetaxel [37], Topotecan and Cyclophosphamide [38] and Irinotecan and Temozolomide [39].



### 36.5.3 Osteosarcoma

Osteosarcomas are primary malignant tumors of the bone, characterized by the production of osteoid or immature bone by malignant cells [40]. Although rare, osteosarcoma is the most common primary neoplasm of bone in children and adolescents and the fifth most common malignant disease among adolescents and young adults [41]. In adults older than 65 years, osteosarcoma develops as a secondary malignancy related to Paget's disease [4]. In general, osteosarcoma is classified into three histological subtypes: intramedullary, surface and extraeskeletal [42].

Although osteosarcomas produce a favorable response to chemotherapy, surgery is essential when a curative treatment is intent [43]. The specific surgical procedure is dictated by the location and extent of the primary tumor [44].

The survival of patients with osteosarcomas has improved dramatically in the last 40 years, and this is due to the use of effective chemotherapy. Prior to the routine use of systemic therapy for conventional osteosarcoma, 80–90% of the patients developed metastases despite local tumor control and died of their disease. It was surmised that at diagnosis most patients already present with micrometastases, which can be successfully eradicated if chemotherapy was administered at a time when the disease burden is low [45]. Chemotherapy plays small role in the management of patients with low grade osteosarcoma or surface [2].

The right time for administration of chemotherapy (pre or postoperative) has not been defined, as there is no difference in survival between the two forms. Neoadjuvant chemotherapy is particularly preferred when a limb sparing procedure is intent [46].

There is no a global consensus about a standard chemotherapy regimen for osteosarcoma. Most of the current regimens use Doxorubicin and Cisplatin with or without high-dose Methotrexate (HDMTX) [47]. The combination of Doxorubicin and Cisplatin is most often offered for older patients [48]. However, the tolerability of high doses of Cisplatin and the role of HDMTX remain unanswered questions. A methotrexate-containing regimen is a reasonable standard of care in this population, if patients can tolerate it. Options include a five-week cycle of cisplatin (100 mg/m<sup>2</sup> day 1) and doxorubicin (25 mg/m<sup>2</sup> days 1–3), followed by two weekly doses of HDMTX (6–12 g/m<sup>2</sup> with leucovorin rescue), with 3 cycles administered preoperatively and three postoperatively [47].

Osteosarcoma is considered relatively resistant to radiation therapy. Primary radiation therapy is often inadequate to achieve local control. Whenever possible, surgery is preferred for local control. For patients with tumors in challenging axial sites (skull, spine, sacral base), radiotherapy may be a local control option when surgery is not performed [49].

The prognosis of patients presenting with metastatic disease is poor, contrasting with patients with localized disease [50]. The localization of metastases has prognostic importance, with better results for patients with lung-only metastases [47], and the ability to control all sites of macroscopic disease is essential for successful treatment [51].

There is no single standard approach for the management of patients with metastatic osteosarcoma at diagnosis. The most active drugs are the same used in the metastatic disease setting, however, with low response rates and survival [51].

For patients with resectable metastases at presentation, neoadjuvant chemotherapy is recommended, followed by resection of the primary tumor. Chemotherapy and metastasectomy are included as options for the management of metastatic disease [52].

About 30% of patients with localized disease and 80% of patients with metastatic disease will fail. Some factors may be considered as having a better prognosis, such the presence of single metastases, relapse time and the possibility of complete resection of the metastases [53]. Patients who are not candidates for surgical resection of metastases should be considered for palliative treatment with radiotherapy or chemotherapy [54]. In this setting, combinations of ifosfamide (3 g/m<sup>2</sup>/day) and etoposide (75 mg/m<sup>2</sup>/day) for 4 days are more active than other agents alone [55]. Cyclophosphamide plus etoposide or gemcitabine plus docetaxel are other options available [56, 57].

## Questions

### 1. These conditions increase the risk of developing bone sarcomas, except:

- (a) Paget's disease of bone
- (b) Previous fractures (Answer)
- (c) Fibrous dysplasia
- (d) McCune-Albright syndrome

Comment: Some benign conditions increase the risk of developing bone sarcomas, such as Paget's disease of bone, fibrous dysplasia, McCune-Albright syndrome and Mazabraud's syndrome. Even nononcological conditions such as chronic osteomyelitis and bone infarcts may progress to sarcomas. The only factor that is not related to the increase the risk of developing of bone sarcomas is the existence of a previous fracture.

### 2. Among the environmental factors following, it's related to the increased risk of developing osteosarcoma:

- (a) Ionizing radiation (Answer)
- (b) Smoking
- (c) Alcoholism
- (d) Obesity

Comment: Environmental factors are also known as involved in the genesis of osteosarcomas, such as ionizing radiation, responsible for approximately 3% of cases of bone sarcomas. There are no sufficient data to relate the others factors to the development of osteosarcomas.

### 3. Among the laboratory tests below, all may be altered in patients with osteosarcoma, except:

- (a) Lactate dehydrogenase
- (b) Alkaline phosphatase

- (c) Calcium (Answer)
- (d) Erythrocyte sedimentation rate

Comment: In patients with bone sarcomas, laboratory abnormalities are not very frequent except for elevations in alkaline phosphatase, lactate dehydrogenase, and erythrocyte sedimentation rate.

**4. About chondrosarcomas, mark the true alternative:**

- (a) They are more frequent tumors in children
- (b) The most are high grade tumors
- (c) They are tumors that never metastasize
- (d) They are not responsive to chemotherapy (Answer)

Comment: Chondrosarcoma occurs most frequently between 40 and 70 years of age. About 90% of chondrosarcomas are low grade tumors and they rarely metastasize. Chondrosarcomas are considered chemoresistant tumors, and this characteristic can be attributed to factors such as slow growth, drug resistance genes expression, difficulty of drugs accessing the tumor.

**5. Radiotherapy may be useful in the management of chondrosarcomas in all of the following alternatives, except:**

- (a) After a complete resection, in the adjuvante context (Answer)
- (b) After an incomplete resection of a high-grade chondrosarcoma
- (c) When the resection is not feasible
- (d) When the resection would cause an unacceptable morbidity

Comment: Radiotherapy can be beneficial after an incomplete resection of a high-grade chondrosarcoma and in the palliative context, such as in situations where resection is not feasible or would cause an unacceptable morbidity. There is no benefit for treatment with radiotherapy after a complete resection.

**6. Chondrosarcomas are considered chemoresistant tumors. Chose the alternative that not explain this characteristic:**

- (a) Drug resistance genes expression.
- (b) Slow growth
- (c) Tumor heterogeneity (Answer)
- (d) Difficulty of drugs accessing the tumor

Comment: Chondrosarcomas are considered chemoresistant tumors, and this characteristic can be attributed to factors such as slow growth, drug resistance genes expression, difficulty of drugs accessing the tumor because of large amount of extracellular matrix and poor vascularization and high activity of anti-apoptotic and pro-survival pathways.

**7. About Ewing's sarcoma, choose the right alternative:**

- (a) They are high grade tumors (Answer)
- (b) They share a common rearrangement of genes involving the EWS gene on chromosome 19

- (c) They are the most common bone cancer
- (d) They are more common in elderly people

Comment: All Ewing's Sarcomas are high grade tumors. Molecular biology studies have shown that almost all of these tumors share a common rearrangement of genes involving the EWS gene on chromosome 22, and in most cases it is a recurrent chromosomal translocation, t [11, 22](q24;q12). Ewing's Sarcoma is the third most common bone cancer and the incidence is higher in the second decade of life and young adults.

**8. About the use of chemotherapy in treatment of Ewing's sarcomas:**

- (a) Routine use of chemotherapy did not alter the prognosis of the disease
- (b) Because it is a high-grade tumor, has a good response to chemotherapy (Answer)
- (c) Chemotherapy is always used in the adjuvant setting
- (d) The use of multidrug therapy does not increase the benefit compared to monotherapy

Comment: Before routine chemotherapy use, almost all patients early diagnosed Ewing's Sarcomas developed distant metastatic disease and eventually died, because this is considered a systemic disease. Chemotherapy can successfully eradicate occult metastases, and current treatment plans include chemotherapy, usually given before and after local treatment, and the standard treatment includes the use of multiple drugs, including Vincristine, Doxorubicin and Cyclophosphamide (VDC) in alternating cycles with Ifosfamide and Etoposide (IE).

**9. Indicate the most appropriate treatment for a patient diagnosed with Ewing sarcoma of the scapula, without evidence of metastatic disease:**

- (a) Surgery
- (b) Surgery followed by radioterapy
- (c) Preoperative chemotherapy (with vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide), followed by surgery and adjuvant chemotherapy (Answer)
- (d) Preoperative chemotherapy (with vincristine, doxorubicin and cyclophosphamide), followed by surgery and adjuvant chemotherapy.

Comment: Current standard treatment includes Vincristine, Doxorubicin and Cyclophosphamide in alternating cycles with Ifosfamide and Etoposide. Cycles are repeated every 2 weeks for 4–6 cycles before the local therapy and, after local treatment, additional cycles of the same treatment are given postoperatively for a total of 14–17 cycles. The local treatment can be surgery, radiation or both. There are no randomized trials comparing RT and surgery for local control, however, some retrospective series and a systematic review suggest superior local control with surgery.

**10. About osteosarcomas, choose de right alternative:**

- (a) Osteosarcomas are more common in elderly
- (b) In elderly, osteosarcoma can be related to Paget's disease (Answer)
- (c) Osteosarcoma is the third most frequent bone neoplasm
- (d) Osteosarcomas are always low grade tumors

Comment: Osteosarcoma is the most common primary neoplasm of bone in children and adolescents and the fifth most common malignant disease among adolescents and young adults. Oteosarcomas can be low-grade tumors, with better prognosis, or high-grade tumors, with poor prognosis. When osteossarcoma affects the elderly, it can be related to Paget's disease.

**11. About the role of chemotherapy in the treatment of osteosarcoma, choose the correct alternative:**

- (a) The use of chemotherapy does not significantly alter the evolution of patients with osteosarcoma
- (b) Chemotherapy reduces the chance of local recurrence of osteosarcomas
- (c) Routine use of chemotherapy dramatically reduced relapses at a distance (Answer)
- (d) Chemotherapy has an important role in the treatment of low grade osteosarcomas

Comment: The survival of patients with osteosarcomas has improved dramatically in the last 40 years, and this is due to the use of effective chemotherapy, because chemotherapy reduces de risk of distant recurrence. Chemotherapy plays small role in the management of patients with low grade osteosarcoma or surface.

**12. Consider a 28-year-old patient with high-grade osteosarcoma in the left tibia with no evidence of distant metastases. Choose the best treatment strategy for this patient:**

- (a) Surgery
- (b) Radiochemotherapy
- (c) Surgery followed by adjuvant chemotherapy with Cisplatin and Doxorubicin
- (d) Neoadjuvant and adjuvant chemotherapy with Cisplatin, Doxorubicin and high doses of Methotrexate (Answer)

Comment: The right time for administration of chemotherapy (pre or postoperative) has not been defined, as there is no difference in survival between the two forms. Neoadjuvant chemotherapy is particularly preferred when a limb sparing procedure is intente. There is no a global consensus about a standard chemotherapy regimen for osteosarcoma, most of the current regimens use Doxorubicin and Cisplatin with or without high-dose Methotrexate.

**13. About radiotherapy in treatment of osteosarcoma, check the right alternative:**

- (a) Radiotherapy is indicated for adjuvant treatment

- (b) Osteosarcomas are considered relatively radioresistant
- (c) It can be indicated for local control in tumors which surgery is contraindicated (Answer)
- (d) Radioterapy is an option to surgery for local control

Comment: Osteosarcoma is considered relatively resistant to radiation therapy. Primary radiation therapy is often inadequate to achieve local control. Whenever possible, surgery is preferred for local control. For patients with tumors in challenging axial sites (skull, spine, sacral base), radiotherapy may be a local control option when surgery is not performed.

**14. All of the following are considered to be the best prognostic features in metastatic osteosarcoma, except:**

- (a) Early relapse (Answer)
- (b) Single metastase
- (c) Pulmonary metastases only
- (d) Possibility of complete resection of metástases

Comment: Are considered as having a better prognosis the presence of single metastases, relapse time and the possibility of complete resection of the metastases. Early relapse is an indicator of poor prognosis.

**15. What is the best treatment strategy for a 19-year-old patient with osteosarcoma of umero with 2 lung resectable lung metástases?**

- (a) Chemotherapy only
- (b) Neoadjuvant chemotherapy, followed by surgery and adjuvant chemotherapy (Answer)
- (c) Surgery followed by adjuvant chemotherapy
- (d) Surgery only

Comment: For patients with resectable metastases at presentation, neoadjuvant chemotherapy is recommended, followed by resection of the primary tumor and adjuvant chemotherapy.

**Related Clinical Case**

A 34-year-old male patient in investigation for backache, associated with anemia and left thigh mass for about 6 months and weight loss of 9 kg in this period, presents with medullary compression syndrome, with paraparesis and urinary retention. MRI of the spine was performed, showing marginal bone irregularity L5 – S1 and protrusion with dural sac compression, hypersignal in L3 – L4, L4 – L5, L5 – S1. Patient was hospitalized and submitted to surgical procedure for decompression of the spinal cord with thoracic spine arthrodesis. In the occasion, a biopsy of the bone lesion was performed. The anatomopathological examination revealed small blue and round cell neoplasm and immunohistochemistry showed positivity for Vimentina and CD 99, compatible with Ewing's Sarcoma. MRI of left thigh showed heterogeneous expansive formation in the proximal and middle diaphyseal region of the left femur, with irregular thickening and permeation pattern

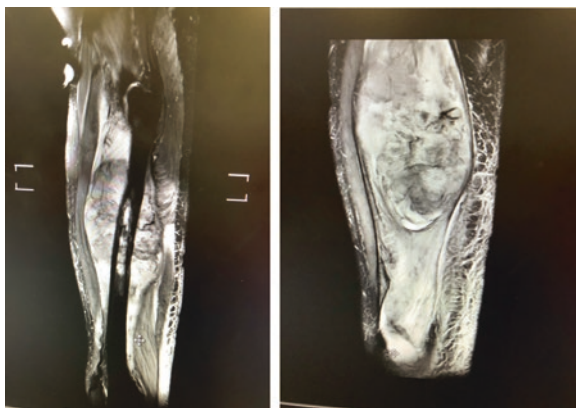
of the cortical bone, presenting a massive soft tissue component involving the part of the musculature of the posterior and medial compartments, and mainly anterior, infiltrating the medial, lateral and intermediate vastus muscles, measuring  $19 \times 12 \times 9$  cm (L  $\times$  AP  $\times$  LL), establishing close contact with medial bulging of the femoral neurovascular bundle. Other nodular lesions with similar characteristics are observed in the right pubis, posterior region of the left femoral head, and the largest in the minor trochanter measuring  $4.5 \times 3.3 \times 2.3$  cm, which within the clinical context may represent secondary involvement. Prominent lymph nodes with globular morphology in the left inguinal chain, measuring up to 1.6 cm. Diffuse edema alteration with edema pattern of the adductor regions and thigh compartments, especially of the extensor musculature, associated to diffuse edema with thickening of the fibroadipous septa of the subcutaneous tissue predominating on the lateral and posterior side of the thigh (Fig. 36.1).

Bone scintigraphy showed hyperconcentration of the radiopharmac in the projection of the cranial calotte (Bone parietal E), thoracic spine (T9, 10 and 12) and heterogeneous distribution of the radiopharmac in the projection of the proximal 2/3 of the left femur. Chest, abdomen and pelvis tomography showed secondary osseous lesions in T5, T10 and T12 and left iliac bone. There was no visceral lesions.

After bone marrow decompression, the patient maintained an important low back pain, paraparesis of the lower limbs and urinary and fecal incontinence.

It was decided to start systemic treatment with chemotherapy with the VDC scheme (Cyclophosphamide  $1200 \text{ mg/m}^2$  + Doxorubicin  $75 \text{ mg/m}^2$  + Vincristine  $2 \text{ mg}$  with cycles every 21 days). After the first cycle, patient had improvement of the pain. After the second cycle had improvement of urinary and fecal incontinence. New staging after C3 showed reduction of the mass in the left thigh, now with  $15 \times 10 \times 7$  cm. The patient received local control with radiotherapy of the primary and metastatic disease at week 9. The systemic treatment was maintained, and the patient presented important clinical improvement, with recovery of the muscular strength in the gradual and progressive lower limbs. After a cumulative dose of  $375 \text{ mg/m}^2$  doxorubicin was replaced by dactinomycin. After administration of C8

**Fig. 36.1** Imaging assessment



the patient was staged, maintaining the response in the left thigh mass (now with  $9 \times 8 \times 5$  cm). The treatment was maintained for 17 cycles. After that, with physiotherapeutic treatment, patient completely recovered the muscle strength in the lower limbs and had improve of the fecal and urinary incontinence, in addition to improving pain and recovering functionality.

After 12 months of follow-up, the patient maintains stable disease, with no evidence of visceral disease and with controlled osseous lesions.

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# Chapter 37

## Gastrointestinal Stromal Tumor (GIST): Diagnosis and Treatment



Attila Kollár, Pedro Nazareth Aguiar Jr., Nora Manoukian Forones,  
and Ramon Andrade De Mello

**Abstract** Gastrointestinal stromal tumor is the most common mesenchymal neoplasm arising the gastrointestinal tract. The primary tumor is most common in the stomach (60–70%), followed by the small intestine (20–25%), colon and rectum (5%), and esophagus (less than 5%). The median age at diagnosis is between 60 and 65 years. Histologically, GIST is characterized by its immunopositivity for CD117 (KIT). Clinically, there is a paucity of specific symptoms and a majority of cases becomes symptomatic after local compression caused by tumor mass. Surgery is the main treatment for localized disease. The indication for adjuvant imatinib is based upon risk factors such as primary tumor site, tumor size and number of mitosis. KIT-targeted tyrosine kinase inhibitors (TKI) are the cornerstone for the treatment of metastatic disease. Imatinib is the drug of choice in the first-line setting. Sunitinib, regorafenib, and pazopanib are studied further-line treatment options. Immunotherapy studies are ongoing for TKI-refractory patients.

**Keywords** Gastrointestinal stromal tumors · Molecular targeted therapy · Surgery

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## Abbreviations

GIST:	Gastrointestinal Stromal Tumor
PDGFRA:	Platelet-derived Growth Factor Receptor Alpha
NF-1:	Neurofibromatosis type I
SDHB/C/D:	Succinate Dehydrogenase Complex Subunit B, C or D
RTK:	Receptor Tyrosine Kinase
SMA:	Smooth Muscle Actin
SCF:	Stem Cell Factor
DOG1:	Discovered on GIST
SDH:	Succinate Dehydrogenase
ESMO:	European Society for Medical Oncology
CT:	Computed Tomography
MRI:	Magnetic Resonance Image
PET:	Positron Emission Tomography
AFIP:	Armed Forces Institute of Pathology
NIH:	National Institutes of Health
HPF:	High Power Fields
NA:	Not Available
EUS:	Endoscopic Ultrasound
RFS:	Relapse-free Survival
SSG:	Scandinavian Sarcoma Group
CI:	Confidence Interval
ATP:	Adenosine Triphosphate
NCCN:	National Cancer Comprehensive Network
TSH:	Thyroid-Stimulating Hormone
BSC:	Best Supportive Care
TAM:	Tumor-associated macrophages
CTLA-4:	Cytotoxic T-lymphocyte Associated Protein 4
PD-1:	Programmed-death Receptor 1
PD-L1:	Programmed-death Receptor Ligand 1
ITT:	Intention-to-treat
RECIST:	Response Evaluation Criteria In Solid Tumors

### 37.1 Definition

GIST is the most common mesenchymal tumour in the gastrointestinal tract. GIST is generally characterised by immunopositivity for CD117 (KIT) and arises from interstitial cells of Cajal that are normally part of the autonomic nervous system of the intestine.

## 37.2 Epidemiology

GIST represents the most frequent mesenchymal tumour in the gastrointestinal tract, representing 1–3% of gastrointestinal malignancies [1, 2]. The annual incidence of GIST is approximately 15 per million per year [3]. The incidence has dramatically increased in the last decade mostly due to improved histopathologic detection and greater awareness, although the true incidence may also be increasing [4]. More recent data suggest that the frequency of incidentally detected subcentimetre gastric GIST lesions may be much higher than expected [5].

The median age is approximately 60–65 years [6, 7]. However, GIST has been reported in all age groups but is extremely rare in children. In the young subpopulation, GIST represents a distinct subtype, characterised by female predominance and the absence of KIT/platelet-derived growth factor alpha (PDGFRA) mutations [8].

There is no clear predilection for either gender, but some data have suggested a slight male predominance [6].

Although most GISTs appear to be sporadic, less than 5% occur as part of hereditary familial syndromes either with mutations in the KIT gene or in the form of idiopathic multitumour syndromes such as neurofibromatosis type I (NF-1), the Carney triad (GIST, paraganglioma and pulmonary chordomas) and the Carney-Stratakis-syndrome (dyad of GIST and paraganglioma) [9–11] (Table 37.1).

In adult patients, approximately 60% of GISTs occur in the stomach and 30% in the small intestine. Other sites of origin are the colon, including the rectum, in approximately 5% and the oesophagus in approximately 1% of adult patients.

**Table 37.1** Characteristics of sporadic and hereditary GIST

	Sporadic GIST	Familial GIST	Carney's Triad	Carney-Stratakis-Syndrome	NF-1
Median age	~60 years	~40-50 years	< 35 years	< 25 years	~ 50 years
Gender predilection	No	No	w > m	No	No
Associated symptoms	No	Hyperpigmentation, urticaria pigmentosa, mastocytosis, dysphagia	Paraganglioma, pulmonary chordoma	Paraganglioma	Neurofibroma, skin changes
Mutations	No germ line mutations	KIT/PDGFRA	Not known	SDHB/C/D	NF1, Neurofibromin
Inheritance	–	Autosomal dominant	–	Autosomal dominant	Autosomal dominant
Histology	Spindle cell > epithelioid > mixed cell	See sporadic GIST	Epithelioid	See sporadic GIST	Spindle cell
Localisation	Stomach, small intestine, rectum, mesenterial, others	Small intestine, stomach, rarely rectum	Stomach	Stomach	Small intestine

Adapted with permission from Ref. [12]

Rarely, GISTs develop outside the gastrointestinal tract in the mesentery, omentum or retroperitoneum. However, most of those extragastrointestinal GISTs are metastatic or may be detached from a gastrointestinal primary source [13, 14].

## **37.3 Histology**

### **37.3.1 Cellular Origin**

Based on their histology, GISTs were originally considered to be derived from smooth muscle. However, they rarely showed clear-cut features of complete muscle differentiation. Additionally, in many cases, their immunophenotypic profile differed from that of leiomyomas arising from other sites (e.g., the uterus or soft tissue). The understanding of GIST biology changed significantly with the identification of the near-universal expression of the CD117 antigen, also known as proto-oncogene *c-kit*, in GISTs in the late 1980s [15]. At that time, it was shown that the interstitial cells of Cajal that are part of the autonomic nervous system of the intestine and that serve a pacemaker function in controlling motility express the KIT receptor [16]. Interstitial cells of Cajal have immunophenotypic and ultrastructural features of both smooth muscle and neuronal differentiation. Because GISTs, like interstitial cells of Cajal, express KIT, interstitial cells of Cajal are thought to be the cell of origin. Additionally, as two-thirds of GISTs express CD34, it is postulated that GISTs originate from CD34-positive stem cells within the gut wall differentiating toward the pacemaker cell phenotype with time [17, 18].

### **37.3.2 Histopathology**

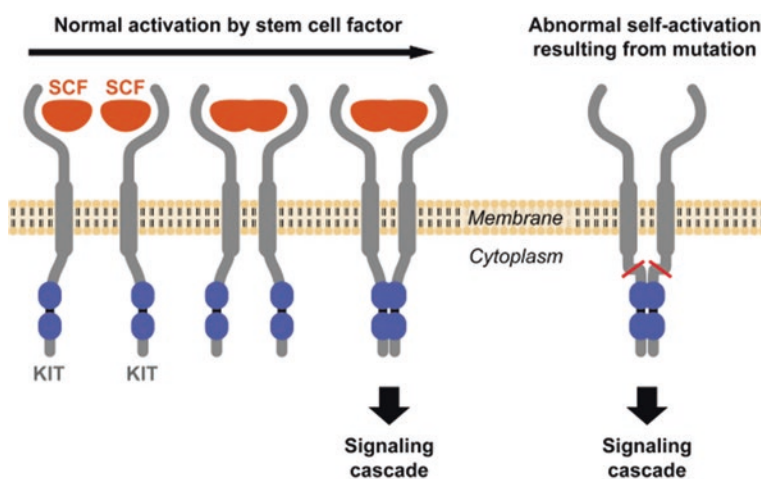
The differential diagnosis of a subepithelial tumor arising in the gastrointestinal tract is broad, and histologic findings observed on haematoxylin and eosin-stained sections are not specific for GIST. The cellular morphology of GISTs is mainly divided into three categories, namely the spindle cell type (70%), epithelioid type (20%) and mixed type (10%) [14, 19]. Whereas gastric, small intestinal and colonic GISTs are mostly composed of spindle cell tumours, KIT-negative GISTs are more often of the epithelioid type [20]. The epithelioid variant may show discohesive, hypercellular, sarcomatous morphology with significant atypia and mitotic activity [21].

### 37.3.3 Immunohistochemical Features

#### KIT-positive GIST:

A significant breakthrough was the discovery that most GISTs show strong positivity for CD117 (KIT) in contrast to leiomyomas, true leiomyosarcomas and other spindle-cell tumors of the GI tract, which were typically CD117 negative [22]. CD117 is an antigen that is part of the KIT transmembrane receptor tyrosine kinase (RTK) family and is the product of the KIT proto-oncogene (also denoted *c-kit*). In more than 80% of GISTs, a mutation in the KIT gene leads to a structural variant of the KIT protein, which is abnormally activated and plays an essential role in cell survival, proliferation and differentiation. When KIT binds to its ligand, it forms a dimer that activates its intrinsic tyrosine kinase activity that, in turn, phosphorylates and activates signal transduction molecules that propagate the signal in the cell (Fig. 37.1).

Immunohistochemically, most GISTs (>90%) show strong positivity for CD117 and usually negativity for desmin and S-100, which are positive in smooth muscle and neural tumors [23]. Although KIT positivity is a major defining feature for GIST, its expression may not be sufficient for diagnosis. KIT-positive malignancies include metastatic melanoma, angiosarcoma, the Ewing's sarcoma family of tumours, seminoma, and others [24]. Other commonly expressed markers of GIST include CD34 antigen (70%), smooth muscle actin (SMA; 30–40%), desmin (<5%), and S100 protein (~5%) [25]. In contrast to GIST, leiomyoma and leiomyosarcoma

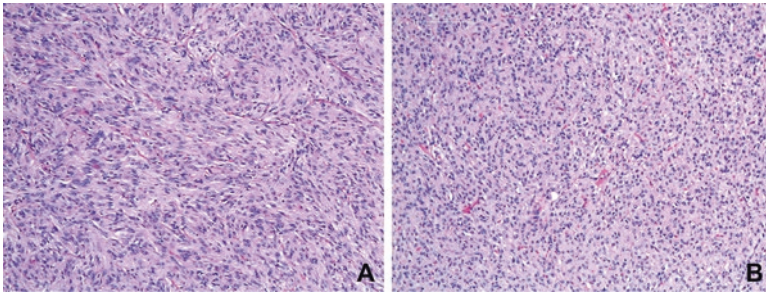


**Fig. 37.1** Activation of KIT. Two KIT receptors normally dimerise in the presence of the ligand stem cell factor (SCF) to initiate downstream signalling (left). Mutations in the receptor cause abnormal constitutive signalling without stimulation from the SCF ligand (right). Hornick JL, MD PhD, Harvard Medical School, Department of Pathology, Boston, MA, and Lazar AJF, MD PhD, Sarcoma Research Center, M. D. Anderson Cancer Center Houston, Texas, reproduced with permission of GIST Support International

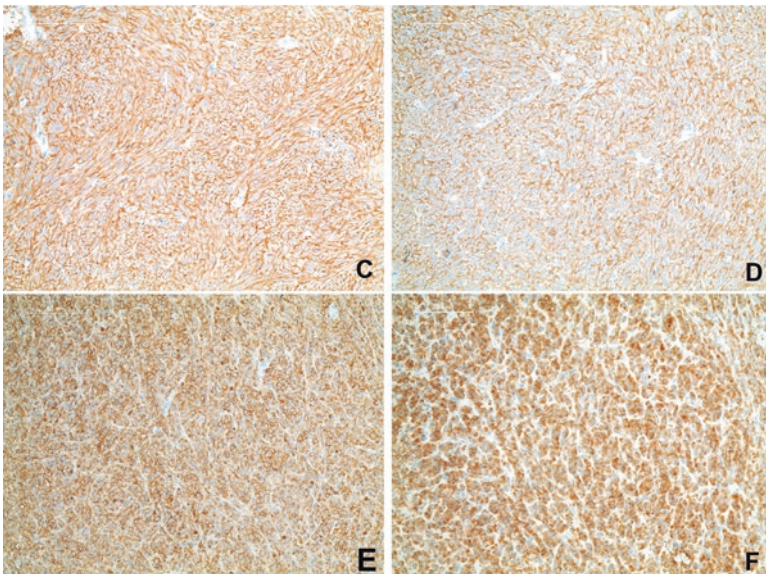
are positive for SMA and desmin and negative for KIT and CD34. Malignant melanoma exhibits diffuse immunoreactivity for S100 protein but can be focally positive for KIT. Schwannomas are strongly and diffusely immunoreactive for S100 protein and negative for KIT [26] (Figs. 37.2 and 37.3).

#### KIT-negative GISTs:

A small subset of GISTs lacks the characteristic KIT mutations [20, 27]. In a proportion of these tumours, activating mutations in the related RTK, PDGFRA,



**Fig. 37.2** Histologic subtypes of GIST. (a) GIST, spindle cell type. (b) GIST, epithelioid type. (Courtesy of Anja Schmitt, MD, Department of Pathology, University Hospital Bern)



**Fig. 37.3** Immunohistochemistry of GIST. (c) Immunohistochemical positivity for c-KIT. (d) Immunohistochemical positivity for DOG-1. (e) Immunohistochemical positivity for CD34. (f) Immunohistochemical positivity for PDGFRalpha. (Courtesy of Anja Schmitt, MD, Department of Pathology, University Hospital Bern)



were detected [28]. Many of these *PDGFRA*-mutant GISTs have an epithelioid morphology. Immunostaining with *PDGFRA* was shown to be helpful in discriminating between *KIT*-negative GISTs and other gastrointestinal mesenchymal tumors [29, 30].

*DOG1*, a calcium-dependent, chloride channel protein, is another highly sensitive and specific marker that often reacts with *CD117*-negative GISTs [31]. *DOG1* expression does not appear to be different between the *KIT/PDGFRA* mutant or wild-type GISTs. Hence, this marker can be used to diagnose *KIT*-negative tumour variants.

Inactivation of the succinate dehydrogenase (SDH) complex appears to be an event shared by sporadic and syndromic GISTs that lack mutations in *KIT* and *PDGFRA* [32]. Immunohistochemical loss of succinate dehydrogenase subunit B (SDHB) has been shown to be a practical marker to identify SDH-deficient GISTs [33].

The experience with these novel immunomarkers (other than *KIT*) is currently limited, and problems exist concerning the quality and availability of the commercial antibodies used to stain for them.

### 37.3.4 Molecular Pathology

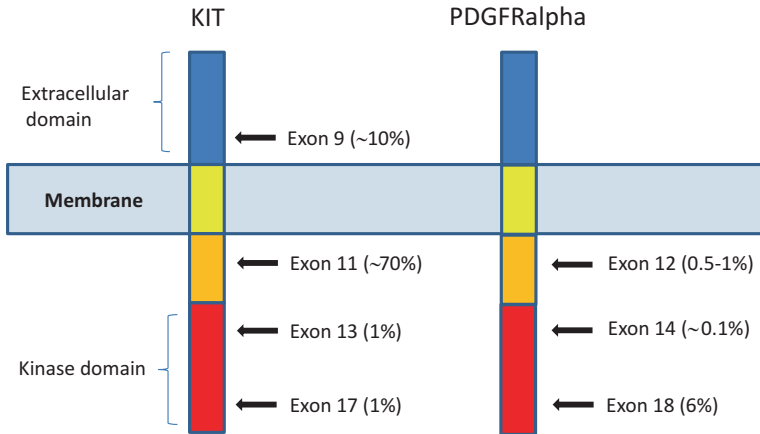
Mutational analysis is an essential diagnostic tool in GIST and plays a key role in the confirmation of the diagnosis and in getting prognostic and predictive, hence treatment-relevant—information.

As noted previously, 95% of adult GISTs overexpress *KIT*, and approximately one-third of *KIT*-negative GISTs express *DOG1*. Therefore, the diagnosis of GIST can be made in most of the cases by observing the macroscopic, microscopic and immunophenotypic characteristics. In cases where the diagnosis of GIST cannot be made based on these features, mutational analysis can be helpful to confirm the diagnosis.

Approximately 80–90% of GISTs have oncogenic mutations, most of them in *KIT* and approximately 6–8% in the *PDGFR* oncogene. Both of these genes are located on the 4q12 chromosome and encode receptor tyrosine kinases. These oncogenic mutations are the reason for the constitutive activation (“gain of function”) of the respective proteins, leading to uncontrolled stimulation of *KIT*- and *PDGFR*-dependent signalling pathways [22].

*KIT* mutations mostly affect exon 11 and, less commonly, exon 9, 13, or 17 [34] (Fig. 37.4).

Oncogenic mutations in GISTs include in-frame deletions, missense mutations and tandem duplications. Notably, different mutations are associated with specific tumour locations and maybe clinically more relevant. The prognosis and treatment response correlate with the underlying kinase genotype. Whereas exon 11 mutations are found in virtually every anatomic region, exon 9 mutations are almost exclusively found in intestinal tumours. Tandem duplications are associated with a gastric



**Fig. 37.4** KIT and PDGFRalpha structure. (Adapted from Corless et al. Annual Review of Pathology: Mechanisms of Disease 2010)

origin and favourable prognosis. Gastric GISTs with exon 11 deletions have a worse prognosis than those with missense mutations [35, 36]. In terms of the response to systemic therapy, patients with exon 11 mutations are more likely to respond to imatinib than those with other mutations (e.g., in exon 9) or those who lack mutations altogether [37].

PDGFR mutations are mainly located in exons 12, 14, and 18 (Fig. 37.3) [38]. A subset of gastric GISTs, particularly tumours with epithelioid morphology, has these types of mutations. The most common mutation is the point mutation D842V, which is relatively insensitive to imatinib although other GIST subtypes confer sensitivity to this agent [28].

GISTs without KIT and PDGFR mutations have been called “wild-type” GISTs, suggesting that these tumours do not have any mutations.

Recently, some GISTs that lack mutations in KIT/PDGFR have been shown to have inactivation or a deficiency in the SDH complex. Somatic and germline mutations in the genes encoding for the B, C, and D subunits of the SDH enzyme have been described in children and adults with sporadic GISTs that are wild-type for KIT and PDGFRA and those arising in the setting of the inherited Carney-Stratakis syndrome [32, 39].

In a very small population of “wild-type” GISTs, activating oncogenic mutations in BRAF and KRAS have been detected. The clinical relevance of those subentities is unknown, although few data suggest the activity of BRAF inhibitors [40, 41].

Hence, the definition of “wild-type” GIST is changing, and the presence of different new molecular markers has been confirmed. A new definition of “wild-type” GIST was proposed at the ESMO Sarcoma Conference 2014, defining this cohort as lacking KIT exon 9, 11, 13, and 17 and PDGFR exon 12, 14, and 18 mutations.

## 37.4 Clinical Presentation

GISTs are associated with a broad range of symptoms. Although many smaller GISTs are detected incidentally during endoscopy, surgery or radiologic imaging, others present with various symptoms. Symptoms and signs are not disease specific but are related more to the site of disease. The most common clinical features are the following:

- Vague abdominal complaints (early satiety, bloating, loss of appetite, nausea, vomiting)
- Fatigue secondary to anaemia
- Gastrointestinal bleeding
- Intraperitoneal haemorrhage
- Symptoms of obstruction
- Symptoms of tumour perforation
- Rarely severe hypoglycaemia due to paraneoplastic tumour production of insulin-like growth factor-2 [42].

Recurrence after primary local treatment is mainly intra-abdominal. The most common site of metastasis is the liver, whereas bone, peripheral skin, soft-tissue and pulmonary metastasis occur much less frequently. Similarly, lymph node metastasis is a very rare condition [43].

## 37.5 Diagnosis and Staging

The primary investigations before the diagnosis of GIST is made are usually upper or lower endoscopy, abdominal ultrasound or CT. In addition to rectal and liver lesions, where local MRI is much more precise in providing diagnostic and preoperative staging information, the initial modality of choice for staging work-up should include contrast-enhanced abdominal and pelvic CT. The initial work-up should be completed using patient history, routine laboratory testing and chest CT or X-ray [44]. The usual CT appearance of GIST is quite specific and is characterised by a solid, smoothly contoured, soft-tissue mass with heterogeneous enhancement. Larger tumors may include varying degrees of necrosis and haemorrhage [45].

GISTs are positron emission tomography (PET)-avid tumors. Although routine PET for staging and follow-up is not yet recommended, it could be useful to differentiate an active tumor from necrotic or inactive scar tissue, to reveal a small metastasis that would have been missed otherwise and to determine when early detection of the tumor response to tyrosine kinase therapy is of special concern [46, 47].

Obtaining adequate tumor tissue material for definitive diagnosis before surgical resection has been challenging. Because these tumors tend to be soft and friable,

biopsy may cause tumour rupture and may be associated with an increased risk for tumor dissemination. Therefore, preoperative biopsy is not generally recommended if the appearance on CT is highly suspicious of GIST, the tumor is resectable tumour, and the patient is operable. Conversely, biopsy might be needed if radiologic characteristics are atypical, and if preoperative therapy is being considered for unresectable or marginally resectable tumors. As percutaneous biopsy carries the theoretical risk of tumor rupture with peritoneal spread of disease, endoscopic ultrasound-guided biopsy is preferred over a percutaneous one [48, 49].

## 37.6 Risk Stratification and Stage Classification

Based on three large retrospective trials performed at the Armed Forces Institute of Pathology (AFIP), the tumor size and mitotic rate were identified as the most important prognostic factors [1, 21, 50]. Because this series represents the largest published GIST cohort with long-term follow-up in the preimatinib era, the data formed the foundation for the National Institutes of Health (NIH) consensus approach to risk stratification of GISTs published in 2002 [25].

Subsequently, evaluating long-term follow-up of even more patients, Miettinen et al. suggested new guidelines for the risk stratification, including the primary tumour site as a relevant prognostic factor considering that anatomic location affects the risk for disease recurrence and progression. When using these tools, it is important to appreciate that the mitotic index and tumor size are non-linear continuous variables, so thresholds should be interpreted wisely (Table 37.2).

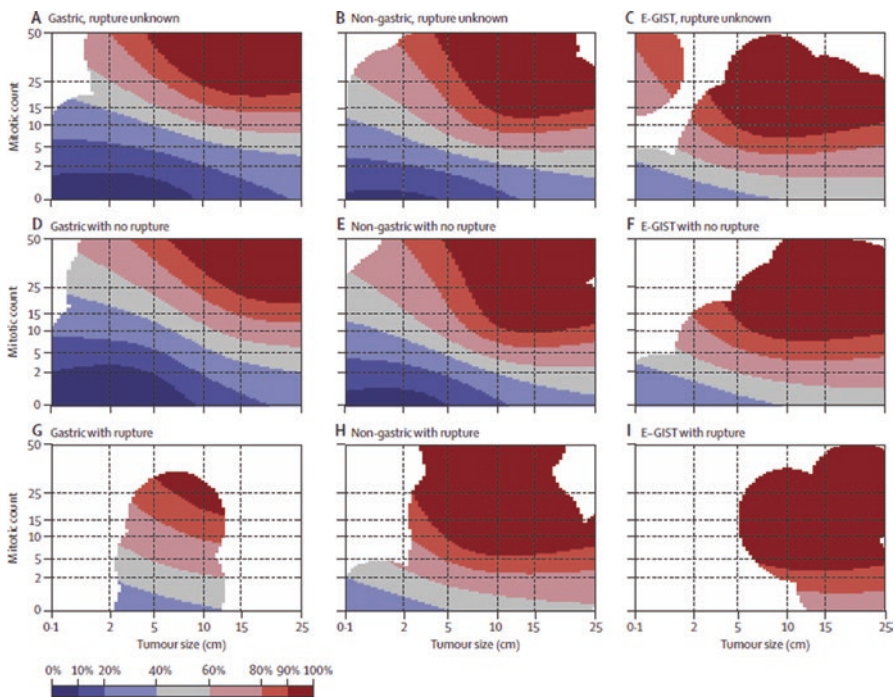
**Table 37.2** AFIP classification

Tumour parameter	Risk for progressive disease (defined as metastasis or tumour-related death)				
	Size (cm)	Gastric	Duodenum	Jejunum or Ileum	Rectum
≤ 5	≤ 2	None (0%)	None (0%)	None (0%)	None (0%)
	> 2 ≤ 5	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	> 5 ≤ 10	Low (3.6%)	Moderate (24%)	n.a.	n.a.
	> 10	Moderate (10%)	High (52%)	High (34%)	High (57%)
≥ 5	≤ 2	None#	High# <sup>a</sup>	n.a.	High (54%)
	> 2 ≤ 5	Moderate (16%)	High (73%)	High (50%)	High (52%)
	> 5 ≤ 10	High (55%)	High (85%)	n.a.	n.a.
	> 10	High (86%)	High (90%)	High (86%)	High (71%)

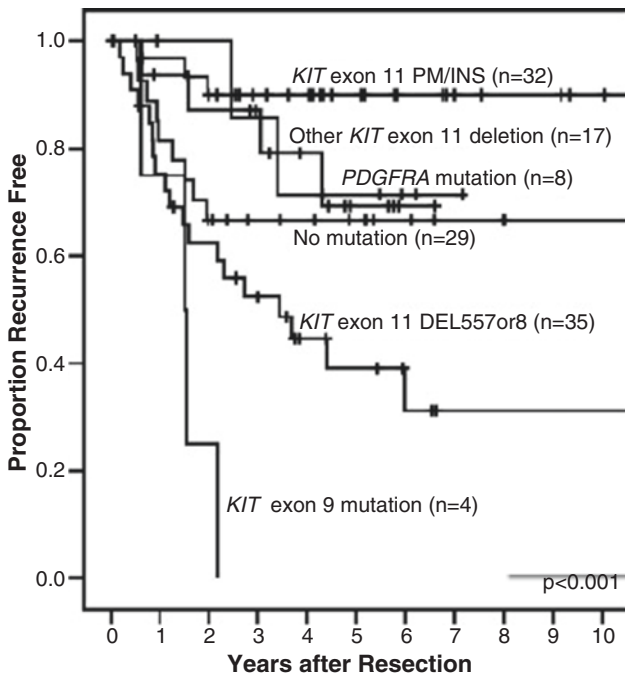
Adapted with permission from Ref. [13]

According to these guidelines, gastric GISTs that are 2 cm or smaller with a mitotic index of 5 or less per 50 HPF can be regarded as essentially benign, but gastric lesions larger than 2 cm with the same mitotic index have a risk for recurrence. Data are lacking on the prognosis of patients with GISTs smaller than 2 cm with a mitotic count of more than 5 per 50 HPF. Additionally, these data confirmed that small intestinal GISTs are more aggressive than gastric GISTs of equal size. This risk classification is an accepted and widely used tool and mainly serves to discriminate patients benefiting from adjuvant systemic therapy [13, 51].

A nomogram was recently published by the Memorial Sloan-Kettering Cancer Center that can be used as an alternative to the risk stratification schema described above. The nomogram can quantify the risk of disease recurrence after complete resection as a continuous variable [52].



**Fig. 37.5** Contour maps for estimating the risk of GIST recurrence after surgery. The upper-row maps are used when the tumor rupture status is unknown (a–c), the middle-row maps are used when the tumor has not ruptured (d–f), and the bottom-row maps are used when tumor rupture has occurred (g–i). Red areas depict high risk, blue areas depict low risk, and white areas indicate a lack of data. The percentages associated with each colour (key) indicate the probability of GIST recurrence within the first 10 years of follow-up after surgery. For example, the middle map of the far left column (d) shows that the 10-year risk of GIST recurrence of a patient diagnosed with a 10-cm gastric GIST with five mitoses per 50 high power fields (HPFs) of the microscope and no rupture is 20–40%. The 10-year risk associated with a similar tumour when the mitosis count is ten per 50 HPFs increases to 40–60%. *E-GIST* extragastrointestinal stromal tumour (arising outside the gastrointestinal tract). (Reprinted with permission from Ref. [54])



**Fig. 37.6** Recurrence-free survival in 127 patients with completely resected localized gastrointestinal stromal tumor (GIST) based on the type of mutation. (Reprinted with permission from Ref. [55])

Tumor rupture, either at surgery or spontaneously, should be regarded an independent risk factor affecting prognosis negatively [53]. Considering this additional risk factor, Joensuu et al. recently proposed a novel, modified risk classification system by generating prognostic heat and contour maps [54] (Fig. 37.5).

Thus far, mutational status has not been incorporated in any risk classification, although some genotypes have a distinct natural history [44, 55] (Fig. 37.6).

Although the TNM classification was published recently, it does not have a clinical impact due to several limitations and, thus, is not recommended [56].

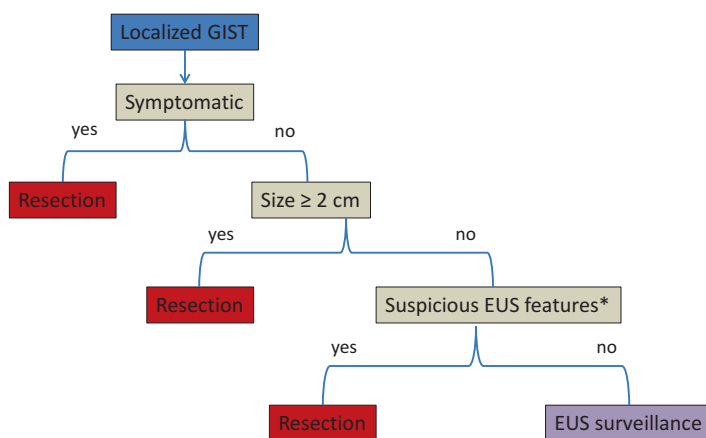
### 37.7 Management of GIST

For optimal management of GIST patients, it is essential to discuss all relevant information, including medical history and laboratory and radiologic findings, within a multidisciplinary team. Pathologists, radiologists, surgeons, and clinical and medical oncologists should be involved in the decision making to ensure the best treatment strategy for each individual with this disease.

### 37.7.1 Primary Local Treatment

Complete surgical removal (R0 excision) of localised GISTs is the mainstay of treatment for potentially resectable tumours with a size  $\geq 2$  cm [57]. Routine lymph node dissection should not be performed because lymph node metastasis is an extremely rare event [58]. Nevertheless, approximately 50% of GISTs will recur [43]. Resection can be performed by traditional open surgery or laparoscopic surgery, although the latter approach should only be performed by surgeons with expertise in the laparoscopic management of cancer and mainly for gastric primaries [59]. The importance of achieving negative microscopic margins is a controversially discussed issue because a negative impact on OS in patients treated with adjuvant imatinib is lacking. However, R1 resection may be associated with a greater risk for recurrence [60]. A re-resection in a R1 situation is not mandatory but may be carried out if functional sequelae are not expected. Depending on the primary tumour site (oesophago-gastric junction, small intestine, rectum), neoadjuvant treatment with imatinib should be considered (see Sect. 37.7.2).

The natural history of small oesophago-gastric and duodenal lesions smaller than 2 cm in size regarding the growth rate and metastatic potential is difficult to anticipate. Many of these lesions will have a very low risk of tumour progression and a low metastatic potential. Endoscopic biopsy may be difficult, and tumour spillage remains a relevant risk. Hence, endoscopic ultrasound assessment and regular follow-up are reasonable in these cases. Should there be any feature of malignant behaviour on ultrasound a resection should also be performed. An algorithmic



\*suspicious endoscopic ultrasound features (EUS):  
Irregular border, cystic spaces, ulceration, echogenic foci, heterogeneity

**Fig. 36.7** Proposed algorithm for the management of localized gastrointestinal stromal cell tumors. (Reprinted with permission from Ref. [49])

approach to the management of gastric GISTs based on size and endoscopic ultrasound (EUS) appearance has been proposed [49] (Fig. 36.7).

### 37.7.2 *Neoadjuvant Systemic Therapy*

The aim of neoadjuvant systemic therapy is to reduce the size of a locally advanced GIST to increase the likelihood of complete resection, reduce surgical morbidity and eventually limit the risk of tumour rupture. Because there are no prospective randomised data, the recommendations on neoadjuvant imatinib therapy are largely based on a few prospective, non-randomised and mainly retrospective studies [61–64].

Eisenberg and colleagues published a prospective phase II RTOG0132/ACRIN6665 trial investigating the feasibility of neoadjuvant imatinib in KIT-positive, resectable  $\geq 5$ -cm primary GIST, or resectable, recurrent GIST. Sixty-three patients received 600 mg/day of imatinib for 8–12 weeks prior to surgery and then continued imatinib for 2 additional years. Among the patients with localised primary disease, only two (7%) had an objective response to preoperative imatinib, but stable disease was achieved in 25 (83%) patients. In 77% of these patients, complete resection could be performed. The present study confirmed the safety of administering imatinib neoadjuvantly, although the treatment period was quite short [61]. Another open-label, single-arm phase II study from Canada investigated neoadjuvant imatinib treatment with 400–600 mg daily in patients with locally advanced or metastatic GIST that was potentially resectable. Imatinib was administered for a maximum of 12 months to a maximal tumour response. Six of 14 patients showed a partial response, and eight showed stable disease; no progressive disease was documented. The median treatment duration was 9 months. Therefore, the authors concluded that the optimal preoperative treatment duration should be between 6 months and 12 months [64].

Taken all together, the data reveal that there is no consensus regarding the indications for neoadjuvant therapy because a particularly treatment benefit was not proven. However, preoperative therapy is a widely accepted concept, particularly in large, bulky tumours of any origin and notably in GIST arising in the oesophagus, oesophago-gastric junction, duodenum and distal rectum, to reduce significant surgical morbidity. Importantly, a biopsy to confirm the diagnosis and exclude imatinib-resistant mutations is mandatory. The treatment response to imatinib should be evaluated early during the treatment course to exclude tumour progression and pre-emptive resection.

To date, questions regarding the imatinib dose in patients with exon 9 mutation and the duration of additive adjuvant treatment in this specific situation remain unanswered, but a total duration of 3 years appears reasonable.



### 37.7.3 *Adjuvant Systemic Therapy*

Although surgery remains the therapeutic modality of choice for localised GIST, the risk of recurrence following complete excision is still eminent. In a recently published analysis of a pool of 2560 patients, including 10 different population-based published series, the estimated 5-, 10-, and 15-year relapse-free survival [RFS] rates were 71%, 63%, and 60%, respectively [54]. This meaningful risk of recurrence is likely due to persistent microscopic disease following surgery. Therefore, the effect of adjuvant systemic treatment with imatinib has been explored subsequently to improve the likelihood of survival in patients with a high risk of recurrence. However, there is no clear consensus from expert groups regarding the level or cut-off of recurrence risk that would justify the use of adjuvant imatinib [44].

After a few phase II trials with very promising results, the benefit of adjuvant imatinib therapy has been evaluated in at least 3 randomised studies.

In the multicentre, randomised, double-blind and placebo-controlled US trial Z9001, 713 patients with a resected GIST and a tumour  $\geq 3$  cm in size were included and patients were randomly assigned to imatinib 400 mg/day or placebo for 1 year. The study was closed after the first interim analysis, which confirmed a significant reduction in recurrence-free survival that was subsequently the primary endpoint. After a median follow-up of 19.7 months, the 1-year RFS rate was 98 versus 83% favouring imatinib, with a hazard ratio for RFS of 0.35 and a 95% CI of 0.22 to 0.53. A benefit in terms of OS could not be confirmed most likely due to cross-over to active treatment and the short duration of follow-up. Imatinib was well tolerated and showed the known toxicity profile (see below) [65]. That pivotal study led to the accelerated approval of imatinib for the adjuvant treatment of completely resected GISTs  $\geq 3$  cm in size. Notably, patients were not stratified according to tumour site and mitotic rate.

The second practise-changing phase III trial was performed by the Scandinavian Sarcoma Group (SSG) XVIII comparing 12 versus 36 months of adjuvant imatinib treatment. Eligible patients were of high risk defined according to the modified consensus criteria as having at least one of the following: a tumor size  $>10$  cm, a mitotic count  $>10/50$  high-power fields (hpf), a tumor size  $>5$  cm with a mitotic rate  $>5/\text{hpf}$ , or tumour rupture. After recruitment of 400 patients with a median follow-up of 54 months, patients in the 3-year arm showed a significant improvement in RFS, the primary endpoint (5-year RFS, 66 versus 48%; HR, 0.46; 95% CI, 0.32–0.65) as well as overall survival (OS, 92 versus 82%; HR, 0.45; 95% CI, 0.22–0.89). Subgroup analysis demonstrated that patients with exon 9 or PDGFRA mutation did not show a treatment benefit. In summary, these data established at least 36 months of adjuvant **imatinib** as a new standard for patients with high-risk GIST [66].

Recently, an abstract of the EORTC 62024 study randomising GIST patients between 2 years of adjuvant imatinib and no adjuvant treatment was presented and showed no significant benefit in the primary endpoint, which was imatinib-free survival, under the intermediate- and high-risk scenario [67]. These results per se

implicate that progression of GIST may be delayed but survival might not be improved with the available TKIs.

A few outstanding questions need further investigation. First, whereas there is a consensus that PDGFRA D842V-mutated GISTs should not be treated with adjuvant therapy due to their lack of imatinib-sensitivity, the treatment dose in patients with exon 9 mutation is a matter of debate and 800 mg/day of imatinib may be used analogous to the evidence in the metastatic tumour stage. However, there are often regulatory problems limiting this practise. Additionally, we could not confirm whether “wild-type” GISTs also benefit from adjuvant therapy considering their lower sensitivity to imatinib and more indolent natural history [37, 38, 68].

Second, the question remains concerning the optimal treatment duration and whether treatment should be continued for longer than 3 years. In the Scandinavian trial from Joensuu et al., in both groups, within 6–12 months of discontinuation of adjuvant imatinib, the rates of disease recurrence were similarly increased [66]. Similarly, we know from the BFR-14 trial, in patients with advanced GIST, that some patients who had a complete response to imatinib relapsed even after 5 years of treatment when therapy was interrupted therapy [62]. Hence, the latter findings raises questions as to whether recurrences are truly being prevented or just delayed and whether the duration of adjuvant therapy should be beyond 3 years. Currently, a phase II, non-randomised, open-label multicentre study is investigating 5 years of adjuvant imatinib therapy in patients at significant risk for recurrence following complete resection of primary GISTs (NCT00867113).

Additionally, the optimal treatment duration in the case of tumour rupture is unknown given the uncertainty concerning whether these patients should be viewed as virtually metastatic.

Finally, there is no consensus concerning the definition of high-risk GIST, which depends on different risk classifications.

## ***37.7.4 Systemic Treatment in the Palliative Setting***

### **37.7.4.1 Cytotoxic Chemotherapy**

Until 2000, the diagnosis of GIST was not well defined. Therefore, trials published before that time included a mixture of so-called GISTs, leiomyosarcoma and different other sarcoma subtypes, indicating meaningless clinical activity in these patients. Since then, a few trials have investigated the efficacy of cytotoxic chemotherapy in specific GISTs, confirming a very low response rate of 0–5% [69–71]. As such, overall, the data strongly support the lack of benefit of cytotoxic agents for the treatment of GISTs. Hence, the use of cytotoxic agents is not recommended in daily practise.

### 37.7.4.2 First-Line Treatment: Imatinib

Imatinib mesylate is a pyrimidine derivative that functions as a specific inhibitor of several tyrosine kinase enzymes, mainly ABL, BCR-ABL, KIT and PDGFR. Imatinib works by binding close to the ATP binding site, locking it and thereby preventing substrate phosphorylation, subsequently leading to the inhibition of signalling pathways involved in proliferation and survival [72, 73].

Many studies have confirmed the impressive benefit of imatinib in metastatic GISTs [74, 75]. The standard dose of imatinib is 400 mg daily. A higher dose level of 600 or 800 mg daily was studied in different randomised trials and have failed to show significantly greater efficacy for higher imatinib doses. Trial data are indicative of more side effects from higher-dose therapy [76–78]. One possible explanation for the failure to demonstrate a benefit from higher imatinib doses is interpatient variability in pharmacokinetic exposure. In a study including 73 patients who were randomly assigned to 400 or 600 mg of imatinib daily, there was a tenfold variance in trough levels with either dose. Clinical outcomes were correlated with steady state trough levels. Trough values below 1100 ng/mL were associated with a significantly shorter time to tumor progression and a lower rate of clinical benefit compared with higher trough levels [79, 80].

Another finding in different imatinib trials was the influence of mutations on the treatment response. For example, in the US Intergroup trial comparing 400 with 800 mg of daily imatinib, patients whose tumors expressed an exon 11 mutant isoform were more likely to have an objective response to imatinib compared with those with an exon 9 isoform or those who had no kinase mutations (72 versus 44 and 45%, respectively). Patients with an exon 11 mutation also had a significantly longer time to disease progression (25 versus 17 and 13 months, respectively) and

**Table 37.3** Imatinib adverse events

Adverse effects	Any grade(%)	Grade 3 or 4(%)
Edema or fluid retention	71,2	1,4
Nausea	50,7	1,4
Diarrhoe	39,7	1,4
Myalgia or musculoskeletal pain	37	0
Fatigue	30,1	0
Dermatitis or rash	24,7	2,7
Neutropenia	8,2	6,8
Abnormal liver-function tests	5,5	2,7

Adapted from Ref. [76]

median overall survival (median 60 versus 38 and 49 months, respectively). However, improved response rates were documented for patients with exon 9–mutant tumors treated with imatinib 800 mg versus 400 mg (CR/PR, 67% v 17%;  $p$  0.02) [81].

Additionally, considering PDGFRA mutations, the D842V subtype was shown to be imatinib resistant, whereas other PDGFRA mutations appear to be imatinib sensitive [82].

In summary, most of the international guidelines (NCCN, ESMO) recommend a treatment start of 400 mg of imatinib. Should mutational analysis be available and exon 9 mutation is found, a starting dose of 800 mg is reasonable if covered by the health insurance. Treatment should be continued indefinitely because treatment interruption is generally associated with an early relapse [62]. The median time to progression on imatinib is approximately 2–3 years [76, 77].

The most common side effects of imatinib include the following (Table 37.3):

Most of these side effects are manageable conservatively. For example, nausea can be mitigated by taking the drug with food, which does not seem to interfere with absorption. Diarrhoea can be managed with loperamide. Rashes are often resolved spontaneously with time. Muscle cramps can be reduced by increased oral fluid intake and electrolyte substitution. Fluid retention represents a very common symptom and can be associated with pleural effusion and ascites. Should supportive treatment of this condition be successful, such as a low-salt diet and/or diuretics, no dose reduction is needed. Nevertheless, the latter can potentially lead to severe **congestive cardiac failure**, which is an uncommon but still a severe side effect [83]. Notably, the toxicity profile may improve with prolonged treatment; importantly, all of these toxicities abate if imatinib is withheld.

The most common haematologic side effects include haematotoxicity and elevated liver function tests. Therefore, regular clinical and laboratory follow-ups are recommended to check the liver parameters. Imatinib is metabolised in the liver by the CYP3A4 enzymatic system. Hence, co-medication with CYP3A4 inhibitors should be avoided, or the imatinib dose should be adapted.

### 37.7.4.3 Second-Line Treatment: Imatinib and Sunitinib

Before altering first-line treatment, it is essential to assess patient compliance to imatinib therapy. Any reasons for noncompliance (i.e., depression, asymptomatic disease, side-effects, or cost) should be evaluated carefully, and a solution should be sought to ameliorate regular imatinib intake [84].

In patients with progressing GISTs and manageable side effects, one therapeutic option is to escalate the dose of imatinib to 800 mg. The efficacy of this approach was investigated in the follow-up reports of different trials. Roughly, one-third of patients who were crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease [85].

Patients who are intolerant of imatinib, progress after a very short time on imatinib (a few months) or progress after long-term imatinib therapy should be switched to sunitinib.

Sunitinib malate is another orally administered multi-targeted receptor tyrosine kinase inhibitor of all PDGFR and VEGF receptors and KIT, among a few others. The evidence for its efficacy comes from an international phase III trial of sunitinib versus placebo. This landmark trial included 312 patients with refractory disease, and the median follow-up was 42 months. Despite a low objective response rate in the sunitinib group (7% partial response), the median time to tumour progression, the primary endpoint, was four fold higher than that in the placebo group (27 versus 6 weeks, respectively). The allowance of cross-over for the placebo group was based on the lack of significant difference in overall survival. The median number of weeks on treatment was 22 [86, 87]. Not surprisingly, the clinical activity of sunitinib is significantly influenced by the specific mutational subtype. Clinical benefit (partial response or stable disease for longer than 6 months) was significantly higher for those with a primary KIT 9 exon (58%) or “wild-type” GIST (56%) than for those with a KIT exon 11 mutation (34%) [81].

Therefore, sunitinib was approved for the treatment of imatinib-refractory or intolerant advanced GISTs.

The main side effects are listed in the following table (Table 37.4).

Most of the sunitinib-related side effects are manageable with temporary withdrawal or dose reductions (37.4 or 25 mg/d). Mucositis can usually be treated with supportive measures and avoiding irritating food. With the routine application of

**Table 37.4** Sunitinib adverse events

Adverse events	Any grade(%)	Grade 3/4(%)
<b>Non-hematological</b>		
Fatigue	34	5
Diarrhoe	29	3
Skin discoloration	25	0
Nausea	24	1
Anorexia	19	0
Dysgeusia	18	0
Stomatitis	16	1
Rash	13	1
Hand-foot syndrome	13	4
<b>Hematological</b>		
Anaemia	62	4
Leucopenia	56	4
Neutropenia	53	10
Thrombocytopenia	41	5

Adapted from Ref. [86]

emollient lotions, hand-foot-syndrome can be improved or even prevented. Additionally, at follow-ups, the focus should be on the close monitoring of hypertension, heart failure, haematotoxicity, proteinuria, hypothyroidism, gastrointestinal bleeding, bowel perforation and delayed wound healing. In patients with a high cardiovascular risk profile, a baseline echocardiogram should be considered excluding left ventricular dysfunction, which was recorded in approximately 8%. In patients with a history of QT interval prolongation, sunitinib should be used cautiously, and electrolytes should be monitored and substituted if necessary. Hypothyroidism is a very common toxicity recently documented in 62% of GIST patients [88]. Its risk increases with treatment duration. Therefore, TSH levels should be checked every 3–6 months. For planned surgical procedures, sunitinib treatment should be interrupted roughly 1 week before surgery and continued after adequate wound healing has occurred. As sunitinib is also metabolised by CYP3A4, concomitant drug interactions should be evaluated.

#### 37.7.4.4 Mechanism of Resistance to Imatinib and Sunitinib

The development of drug resistance belongs to the natural history of neoplastic diseases. The armamentarium of tumour cells to survive is immense. Intrinsic (or primary) imatinib resistance is defined as an absence of objective response or disease stabilisation lasting less than 3–6 months. Resistance is most commonly related to the primary GIST genotype and is clinically present in approximately 10–15% of patients. Most of these patients will have imatinib-resistant KIT exon 9 or PDGFRA exon 18 D842V mutations or no detectable mutation [27, 38, 81].

Acquired (or secondary) resistance is observed in initially responding or stable GIST and develops at a median time of 18–24 months. The most commonly identified mechanism is the emergence or acquisition of secondary KIT mutations in exons 13, 14 or 17. These sites represent the ATP binding pocket and kinase activation loop of KIT [81].

Secondary mutations have been identified in 40–80% of tumour biopsy samples obtained from patients progressing on imatinib and are more common when the patient has a primary KIT exon 11 mutation [89–91]. Polyclonal resistance mechanisms are commonly identified. Coexisting distinct resistance mutations at an inter-lesional and intra-lesional level have been demonstrated to occur in as many as two-thirds of tested patients [92]. Other identified mechanisms of acquired resistance have included amplification of KIT and pharmacokinetic resistance that may involve altered activity of drug transporters, induction of the cytochrome P450 CYP3A4 isoenzyme, and poor patient compliance [93–95].

Resistance to **sunitinib** shares similar pathogenetic mechanisms to those identified in **imatinib** failure, with acquisition of secondary mutations after an extended initial response to the drug [96].

#### 37.7.4.5 Third-Line Treatment: Regorafenib

Regorafenib is another oral TKI targeting a similar spectrum of kinases, including KIT, PDGFR and VEGF receptors. In a phase III trial (GRID trial) including 199 patients, its efficacy was proven. Regorafenib (160 mg once daily for 3 of 4 weeks) was compared with best supportive care (BSC) in patients with advanced GIST following progression or intolerance on imatinib and sunitinib treatment. Regorafenib was shown to improve PFS significantly, 4.8 versus 0.8 months, respectively. Crossover was allowed after progression on placebo (85%). Hence, an OS benefit could not be confirmed. The most common grade 3 side effects were hypertension, hand-foot skin reaction and diarrhoea; however, generally, the toxicities have been shown to be similar to those of other TKIs [97]. Information concerning the potential difference in efficacy regarding mutational status is sparse and very much awaited.

#### 37.7.4.6 Further-Line Treatment

Various other systemic treatment options showing beneficial efficacy have been tested in recent years. Due to low study evidence, which is based on prospective trials with a small sample size but mainly retrospective data, these other treatment options are rarely available because of regulatory issues.

Nilotinib, another second-generation TKI, was investigated in a randomised phase III trial (400 mg b.i.d.) versus BSC, BSC with imatinib and BSC with sunitinib. In the centrally reviewed intention-to-treat analysis (ITT), no difference in PFS could be noted. Because approximately 20% of the patients had more than two lines of previous treatment, a post-hoc analysis was performed through the third-line setting. Although not powered for this analysis, a significant OS benefit of more than 4 months could be documented for the nilotinib group of patients [98].

Sorafenib, a TKI that inhibits KIT, VEGFR and PDGFR-beta, was shown to be beneficial in terms of the disease control rate (68%) in a phase II trial with either **imatinib** or imatinib and **sunitinib**-refractory patients [99]. Additionally, a beneficial effect was also documented in a retrospective cohort in the third and fourth-line settings [100]. Therefore, sorafenib should be suggested as an active drug in further-line treatment.

Pazopanib was investigated in a randomized phase II trial. Eighty-one patients were enrolled. Pazopanib plus best supportive care was compared to best supportive care alone for patients previously treated with imatinib and sunitinib [101]. An improvement in progression-free survival for patients treated with pazopanib could be documented (3.4 months versus 2.3 months; HR 0.59, 95% CI 0.37–0.96). Despite the statistically significant result, the clinical benefit is questionable.

Dewaele and colleagues published *in vitro* results of dasatinib being remarkably effective for the imatinib-resistant PDGFRA(D842V) mutant isoform [101].

Finally, the question was raised whether imatinib rechallenge after therapy with different TKIs should be supported with the goal to target disease clones that

retained sensitivity to imatinib again. The results of a phase III trial showed a significantly greater median PFS for those patients who received imatinib (1.8 versus 0.9 months in the placebo group). Most of the patients were crossed over; hence, the median overall survival was similar in both groups. Although this trial was statistically significantly positive, the results question the clinical relevance of this tiny difference in PFS [102, 103].

#### **37.7.4.7 Future Perspectives: Immunotherapy (New Section Suggested)**

GIST contain tumor-infiltrating lymphocytes and other immune cells that provide an opportunity for developing GIST immunotherapy [105]. The most common tumor-infiltrating inflammatory cells are tumor-associated macrophages (TAMs) and CD3+ T cells. This immune environment should be modulated by imatinib therapy [105]. A study conducted by Balachandran et al. combined imatinib and CTLA-4 inhibitor to treat GIST-bearing mice and found that the therapy significantly decreases tumor size when compared with either treatment alone [106].

The binding of PD-1 on immune cells with PD-L1 on tumor cells inhibits the lymphocytes and it is crucial to the immune escape of neoplasm. Bertucci et al. studied PD-L1 mRNA expression using DNA microarray in 139 untreated localized GISTs and found heterogeneous PD-L1 expression across tumors [107]. PD-L1 expression is higher in low-risk tumors than that in high-risk tumors. As expected, patients with low PD-L1 expression have a higher metastatic risk. Pembrolizumab is a monoclonal antibody against PD-1. A clinical trial of Axitinib, a tyrosine kinase inhibitor, plus pembrolizumab is enrolling patients with advanced sarcomas including GIST (NCT02636725).

#### **37.7.5 Local Treatment in the Palliative Setting**

The role of surgery in metastatic GIST is a controversial issue. There is no randomised data providing a response to whether survival may be lengthened with this approach. However, single-institution retrospective studies document improved long-term disease control compared with historical controls following resection for selected patients with limited metastatic disease and a favourable response to systemic therapy. Additionally, patients with localised progression on systemic treatment seem to benefit from surgery. The rationale behind this approach is to overcome drug resistance and, hence, to eliminate malignant cells with secondary mutations and malignant cells that no longer respond to systemic treatment [104–106].

In addition to surgery, other local treatment options to consider, particularly for liver metastasis, are arterial embolisation, chemoembolisation and radiofrequency ablation [107, 108]. Surgery has little to offer in the setting of generalised progression [109, 110].



In summary, lacking clear evidence, surgical treatment in metastatic GIST may be well considered investigational, and a decision should be made by a multidisciplinary team on a case-by-case basis. Furthermore, resection, even if complete, does not eliminate the need for continued treatment with TKI therapy. Progression-free survival is significantly shorter in patients who discontinue treatment than in those who continue the drug after resection.

### **37.7.6 Role of Radiotherapy**

Until recently, GISTs were indicated to be radioresistant tumour entities. Very little was known concerning the efficacy of radiotherapy in this patient cohort. Several case reports have indicated that radiation can reduce the tumour burden and produce durable local control in locally advanced and metastatic tumours [111]. This impression was confirmed by the reported institutional experience of the Memorial Sloan Kettering Cancer Center and a few others. Heavily pretreated patients with symptomatic tumour manifestations were treated with radiotherapy. At least partial palliation of symptoms was achieved in 94.4% of the tumours, whereas complete disappearance of symptoms was achieved in 44.4% of the tumors. A partial response according to RECIST criteria was observed in 35.3% of tumors, and the response was not assessed using Choi criteria. Stable disease was observed in 52.9% of the tumors [112]. To conclude, this retrospective study shows that radiation is safe and effective and should be considered as a treatment modality in GISTs.

## **37.8 Radiologic Response Evaluation**

Assessing the treatment response in GISTs is very challenging. RECIST criteria, which define the treatment response by measuring the change in tumour size, have been used for a long time. However, GIST lesions experience different morphological changes on systemic treatment. Not only a change in tumour size but a change in tumour density can occur during the treatment course. Even an increase in size as a consequence of intratumoral haemorrhage or myxoid degeneration could be an early clinical marker of antitumor activity. Therefore, an alternative method to evaluate radiographic response was established in recent years. These criteria, called Choi criteria (see below), include both tumour size and density in the radiographic response evaluation. Choi criteria have been shown to correlate significantly better with either disease-specific survival or time to tumour progression than RECIST. The authors concluded that the tumour response for GISTs should preferentially be categorised by Choi criteria than by RECIST. Choi criteria are based on regular follow-up with CT, MRI or contrast-enhanced ultrasound [113, 114] (Table 37.5).

PET/CT is a very useful tool to visualise GIST lesions because of its high glucose metabolism [115]. Nevertheless, the routine use of PET as a staging procedure

**Table 37.5** Modified CT response evaluation: Choi criteria

Response	Definition
CR	Disappearance of all lesions No new lesions
PR	A decrease in size <sup>a</sup> of $\geq 10\%$ or a decrease in tumor density (HU) $\geq 15\%$ on CT No new lesions No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of $\geq 10\%$ and does not meet criteria of PR by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Printed with permission of Ref. [113]

Abbreviations: *CR*, complete response, *PR* partial response, *HU* Hounsfield unit, *CT* computed tomography, *SD* stable disease, *PD* progression of disease, *RECIST* Response Evaluation Criteria in Solid Tumors

<sup>a</sup>The sum of longest diameters of target lesions as defined in RECIST<sup>10</sup>

or for surveillance after resection is not yet recommended. However, PET is highly sensitive in the early assessment of tumour response, and a decrease in the FDG uptake can be observed as early as 24 h after treatment is initiated [116]. In the neoadjuvant treatment setting of borderline resectable GIST, close monitoring is essential. Hence, in this clinical scenario, baseline and follow-up PET are widely accepted to document treatment efficacy.

## 37.9 Follow-Up

There are no published data on what constitutes the optimal routine follow-up after completely resected GISTs, and there is no consensus for this issue. Time to recurrence is mostly dependent on the different prognostic factors such as the mitotic index, tumor site and size. Therefore, risk assessment should guide the choice of the optimal follow-up schedule. High-risk patients generally tend to recur within the first 2 years from the end of adjuvant therapy, whereas low-risk patients may relapse subsequently. For example, the ESMO guidelines recommend CT or MRI every 3–6 months for 3 years during adjuvant therapy for high-risk patients. After cessation of adjuvant imatinib treatment, regular follow-up is suggested to be every 3 months in the first 2 years, every 6 months until 5 years and annually for an

additional 5 years from the discontinuation of adjuvant drug treatment. The value of regular follow-up in the low-risk setting remains unclear; however, if carried out, follow-up is suggested to occur every 6–12 months for approximately 5 years. As relapses mainly present with liver and/or peritoneal metastasis, abdominal imaging should be performed with CT or MRI, considering the harmful cumulative X-ray exposure [44].

### Multiple-Choice Questions

1. What is the most common patient age at GIST diagnosis?

- (a) Up to 20 years
- (b) From 20 to 30 years old
- (c) From 30 to 40 years old
- (d) **From 60 to 70 years**
- (e) Over 70 years

The median age at diagnosis is 63 years.

2. Which portion of the gastrointestinal tract is most commonly affected in GIST?

- (a) Duodenum
- (b) Colon
- (c) Straight
- (d) Appendix
- (e) **Stomach**

60–70% of cases occur in the stomach.

3. Which of the following is positive in GIST?

- (a) CD20
- (b) **CD117**
- (c) S-100
- (d) CD45
- (e) OCT4

CD117 or KIT is characteristic of GIST.

4. What is the most frequent KIT mutation in GIST?

- (a) Exon 9
- (b) Exon 8
- (c) **Exon 11**
- (d) Exon 13
- (e) Exon 17

About three-quarters of cases have a mutation in Exon 11.

5. What is the second most common receptor affected in GIST, after KIT?

- (a) VEGFR
- (b) **PDGFRa**

- (c) EGFR
- (d) IGFR
- (e) HER2

The second most common mutation is in the PDGFR $\alpha$  gene.

6. Which mutation is associated with the best prognosis?
- (a) Exon 9
  - (b) Exon 8
  - (c) **Exon 11**
  - (d) Exon 13
  - (e) Exon 17

Mutation in Exon 11 is associated with an increased overall and progression-free survival.

7. Which mutation benefits from imatinib 800 mg daily in the metastatic setting?
- (a) **Exon 9**
  - (b) Exon 8
  - (c) Exon 11
  - (d) Exon 13
  - (e) Exon 17

Mutation in exon 9 is more sensitive to imatinib in higher doses.

8. Which mutation is resistant to sunitinib?
- (a) Exon 9
  - (b) Exon 8
  - (c) **Exon 11**
  - (d) Exon 13
  - (e) Exon 17

Although its better prognosis, mutation in Exon 11 is more resistant to sunitinib.

9. A 60-year-old patient with a palpable mass in the abdomen underwent biopsy that showed poorly differentiated carcinoma with peritoneal metastasis. He started treatment with FOLFOX. However, a clinical and radiological progression could be documented during chemotherapy. Which immunohistochemistry test could help?
- (a) PSA
  - (b) **KIT**
  - (c) S-100
  - (d) CA 19–9
  - (e) PLAP

Positive KIT confirms diagnosis in virtually all GIST cases and allows treatment changes.

10. Patient with a gastric GIST having the following characteristics: mutation in exon 9 of KIT) 7 cm in size, 8mitosis/50 HPF. What is the recommended adjuvant treatment?

- (a) Follow-up
- (b) Imatinib 400 mg adjuvant for 6 months
- (c) **Imatinib 400 mg adjuvant for 3 years**
- (d) Imatinib adjuvant 800 mg for 3 years
- (e) Imatinib 800 mg for 6 months

The standard adjuvant treatment is imatinib 400 mg for 3 years. Based on the literature the impact of a higher imatinib dose is unclear.

11. Patient with a small intestine GIST received an emergency surgical treatment due to intestinal occlusion. The tumor measured 9 cm and had 3 mitosis/50 HPF. What is the best adjuvant treatment?

- (a) **Follow-up**
- (b) Imatinib 400 mg adjuvant for 6 months
- (c) Imatinib 400 mg adjuvant for 3 years
- (d) Imatinib adjuvant 800 mg for 3 years
- (e) Imatinib 800 mg for 6 months

Adjuvant treatment is defined by primary site, tumor size and presence of mitosis. Urgent surgery is not a risk factor for recurrence.

### **Clinical Case**

A 65 years old woman presented with a 3 months history of gastric pain. On examination mass in the upper abdomen could be palpated. CT scan revealed a 15 cm width gastric mass and several peritoneal metastasis. A CT-guided biopsy was performed and the diagnosed a GIST could be made. Histologically, 15 mitosis per HPF could be documented.

Imatinib treatment 400 mg daily was started and tolerated very well. The first response assessment showed stable disease. She was treated with imatinib for 12 months. After 12 months of treatment, the patient presented with worsening performance status, abdominal pain and anemia and. A CT scan confirmed disease progression (20 cm on the largest axis).

Consequently, imatinib dose was increased to 800 mg. A short-term disease stabilization could be achieved. After a new GIST progression treatment was modified to sunitinib 50 mg 2 weeks-on and 1 week-off. Two months later, a new CT scan showed a slight increase in the main lesion (to 22 cm); however, the patient was not tolerating the treatment.

Therefore, the treatment was changed to pazopanib 800 mg daily. This clinical case illustrates that GIST therapy sequencing.

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# Chapter 38

## Clinical Approaches to the Management of Neuroendocrine Tumours



K. L. Yim, B. M. Thomas, and A. Christian

**Abstract** Neuroendocrine tumours (NET) are a rare and heterogeneous group of tumours. Over two-thirds originate from the gastrointestinal tract, and others include lung, breast, ovary and prostate (Modlin IM, Lye KD, Kidd M: *Cancer* 97(4):934–959, 2003). In 11–14% of cases the primary site is unknown [Hauso O, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Ak C et al: *Cancer* 113(10):2655–2664, 2008]. NET are classified according to their tissue origin, biochemical behavior, and prognosis (Ahlman H, Wängberg B, Jansson S, Friman S, Olausson M, Tylen U et al: *Digestion* 62:59–68, 2012). Functional tumours secrete bioactive peptides and may lead to the development of symptoms including flushing, wheezing, abdominal cramps, diarrhoea, blood pressure disturbance and tachycardia (Dong M, Phan T, Yao JC: *Clin Cancer Res* 18:1830–1836, 2012). Investigations include measurement of 24-h urinary 5-HIAA and chromogranin A. Management is dependent on symptoms at presentation, site of disease and tumour grade. Treatments include surgery for localised disease, ablative therapy, somatostatin analogues, chemotherapy and biological targeted therapy for advanced disease. Most patients present with advanced disease and in patients with metastatic disease median survival is around 24–27 months.

**Keywords** Neuroendocrine tumor · Biomarker · Target therapies

### 38.1 Background

Neuroendocrine tumours (NET) are a rare and heterogeneous group of tumours. Over two-thirds originate from the gastrointestinal tract, and others include lung, breast, ovary and prostate [1]. In 11–14% of cases the primary site is unknown [2]. NET are classified according to their tissue origin, biochemical behavior, and

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prognosis [3]. Functional tumours secrete bioactive peptides and may lead to the development of symptoms including flushing, wheezing, abdominal cramps, diarrhoea, blood pressure disturbance and tachycardia [4]. Investigations include measurement of 24-h urinary 5-HIAA and chromogranin A. Management is dependent on symptoms at presentation, site of disease and tumour grade. Treatments include surgery for localised disease, ablative therapy, somatostatin analogues, chemotherapy and biological targeted therapy for advanced disease. Most patients present with advanced disease and in patients with metastatic disease median survival is around 24–27 months [5].

## 38.2 Epidemiology

NET account for only 0.5% of all malignancies but the incidence is steadily increasing [6]. The Surveillance, Epidemiology and End Results (SEER) Programme (USA) data reported a significant increase in the reported annual age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000). African Americans appear to have the highest overall NET incidence at 6.5 per 100,000 per year [7]. A large case control study in the US found that a family history of cancer increases the risk of developing all NET [8].

## 38.3 Genetics

NET may occur either sporadically or as part of a complex familial endocrine cancer syndrome such as Multiple Endocrine Neoplasia type 1 (MEN1), Multiple Endocrine Neoplasia type 2 (MEN2), Neurofibromatosis type 1 (NF1) or von Hippel-Lindau (VHL) syndrome. MEN is an autosomal dominant condition involving the development of multiple tumours in the endocrine system including the parathyroid, endocrine pancreas, anterior pituitary and adrenocortical glands. In MEN1, the defect is found on the long arm of chromosome 11 [9, 10]. Inactivation of its protein derivative menin results in loss of tumor suppression. MEN2 occurs through dominant activation of the RET protooncogene [11, 12]. NF1 is due to mutations in the *NF1* gene located at chromosome 17 [13]. Diagnostic characteristics include café-au-lait spots, optic glioma, axillary and/or inguinal freckling and benign hamartomas (Lisch nodules). Patients with NF1 syndrome have an increased risk of developing digestive tract NET. Mutations in the VHL tumour suppressor gene predisposes individuals to the development of retinal angiomas, central nervous system hemangioblastomas, clear cell renal cell carcinomas, pheochromocytomas and pancreatic NET [14].

## 38.4 Classification

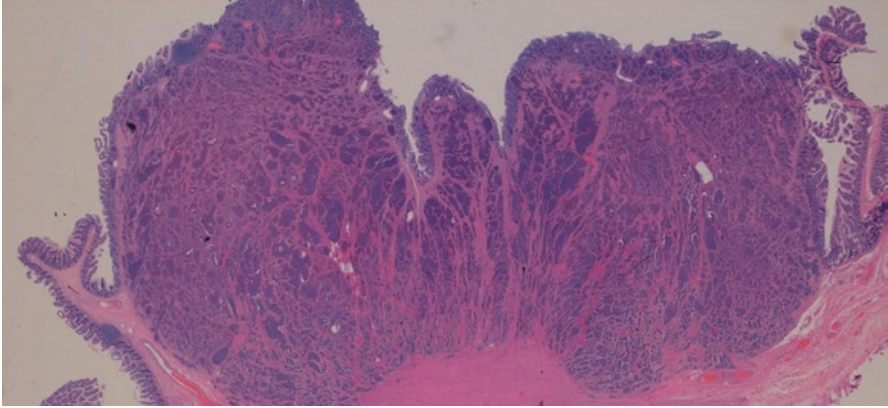
Traditionally, NET were classified according to their embryological origin into tumours of the foregut (bronchi, stomach, pancreas, gallbladder and duodenum), midgut (jejunum, ileum, appendix, right colon) and hindgut (left colon and rectum) [15]. In 2010, the World Health Organization (WHO) updated its classification of NET based on their tissue origin, biochemical behaviour and differentiation [16]. The European Neuroendocrine Tumour Society (ENETS) site-specific T staging relies predominantly on the size of the tumor and the extent of invasion into anatomical structures [17]. NET which originate in the gastrointestinal tract are known as gastroenteropancreatic (GEP)NET, including those from the pancreas (pNET). Tumours may also be classified into those which are functional and secrete bioactive peptides and those which do not (non-functional). Functional tumours are varied according to the peptides they secrete and include gastrinomas (causing the Zollinger-Ellison syndrome), insulinomas, glucagonomas, vasoactive intestinal peptide (VIP)omas and somatostatinomas.

## 38.5 Pathology

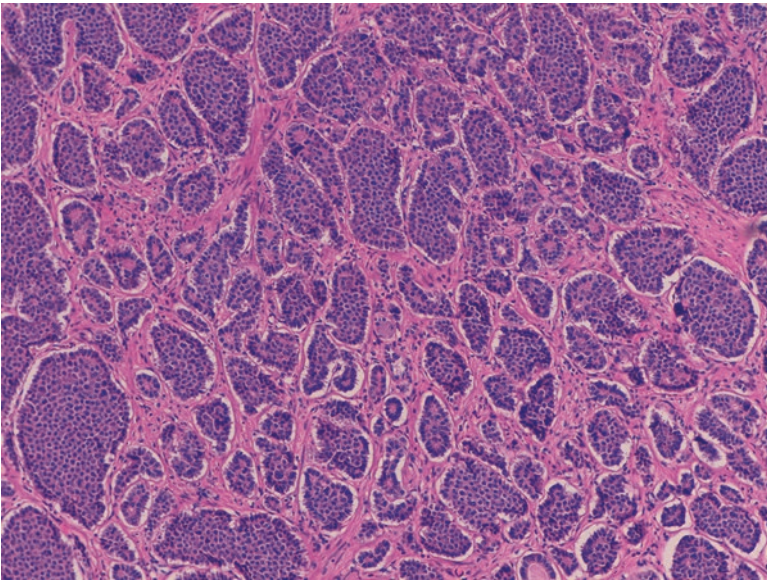
The classification of neuroendocrine tumours, especially in the gastrointestinal tract, including pancreas, has undergone major change recently [18]. Previously all digestive tract NET were grouped together as carcinoids. The term carcinoid is now reserved for the goblet cell carcinoid of the appendix, and is still used for neuroendocrine tumours of the lung. The sub classification and staging of NET can be done a number of ways, with systems presented by the WHO and ENETS groups. At present the Royal College of Pathologist in the UK [19] suggests using the ENETS [20] system primarily, with inclusion of the WHO stage as an additional data item in reports.

The majority of NET in the digestive tract are classified as well-differentiated, that is they have the typical appearance of solid trabecular or gland forming uniform structures, with the classical neuroendocrine cytology. These tumours are what would have been previously called carcinoids. Confirmation of the neuroendocrine nature of the cells is usually undertaken by using 2 or 3 robust markers, and usually a small panel comprising of chromogranin A, synaptophysin and CD56 would be used. (Pictures 38.1, 38.2, 38.3, 38.4, and 38.5)

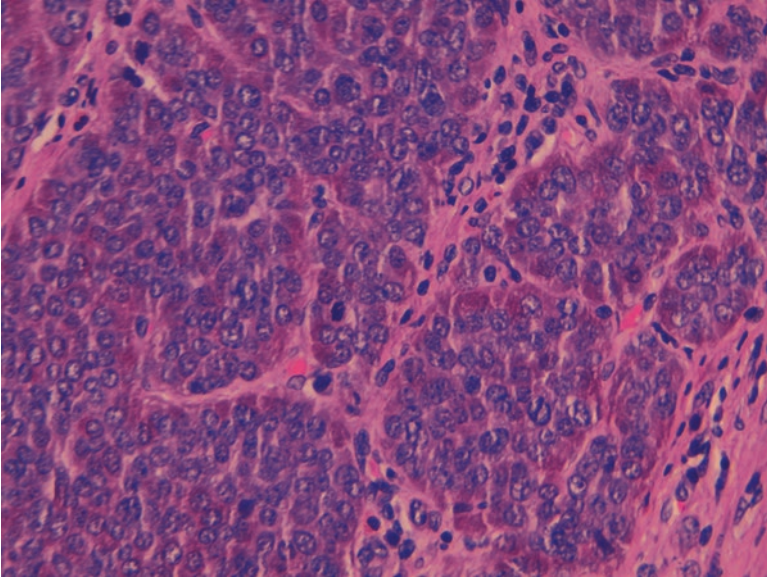
These tumours are then graded using both the mitotic rate (mitoses per 10 high power fields) and Ki-67 proliferation index (immunohistochemical marking of proliferating cells, percentage in a sample of 2000 cells), see Table 38.1 and Pictures 38.6, 38.7, and 38.8.



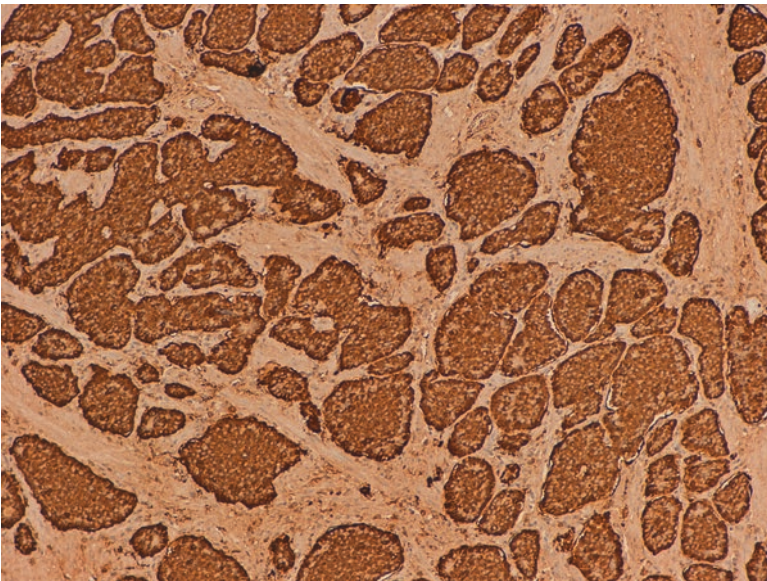
**Picture 38.1** Low power microscopic image of a well-differentiated neuroendocrine tumour in the terminal ileum, showing its polypoid structure and infiltrative base into the wall of the small bowel



**Picture 38.2** Medium power microscopic image of a well-differentiated neuroendocrine tumour in the terminal ileum

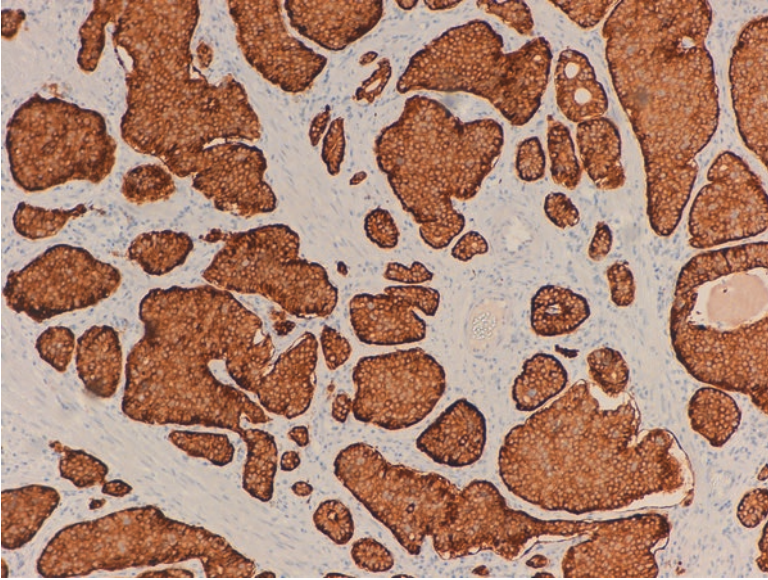


**Picture 38.3** High power image of a well differentiated neuroendocrine tumour with the classical nests of cells with stippled nuclear chromatin, within the cytoplasm there are red staining secretory granules. A single mitoses is seen in the centre of the field



**Picture 38.4** Immunohistochemical marker for chromogranin A, a component of secretory granules

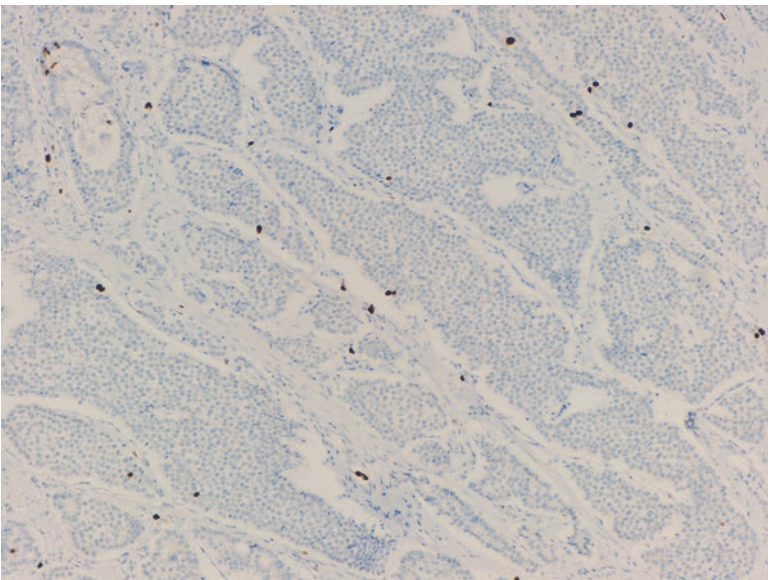




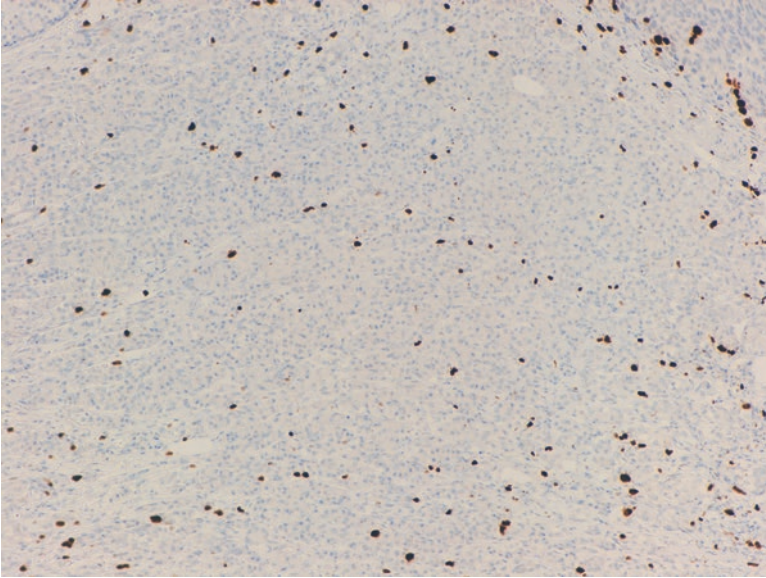
**Picture 38.5** Immunohistochemical marker for synaptophysin, a small vesicle antigen

**Table 38.1** NET pathological grading based on mitotic rate and Ki-67 index

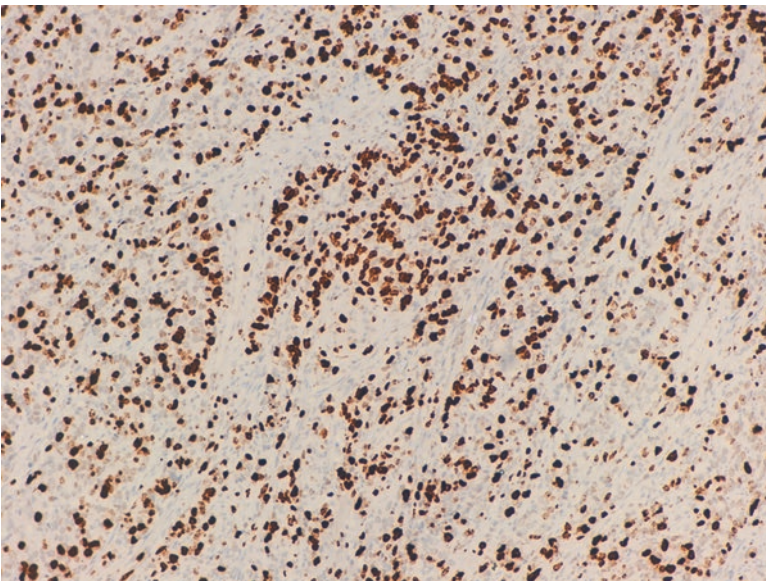
	Grade 1	Grade 2	Grade 3
Mitotic rate per 10 HPF	<2	2–20	>20
Ki-67 index (%) brackets are for pancreatic tumours	≤2 (5)	>2 (5) – 20	>20



**Picture 38.6** Ki-67 labeling of cells in a well-differentiated neuroendocrine tumour, <2% of cells are highlighted (Grade 1)



**Picture 38.7** Ki-67 labeling of cells in a well-differentiated neuroendocrine tumour, >2%, but less than 20% of the cells are highlighted (Grade 2)



**Picture 38.8** Ki-67 labeling of cells in a poorly differentiated neuroendocrine tumour, >20% of cells are highlighted (Grade 3)

At other end of the spectrum are poorly differentiated NET, which have a different histological appearance. Generally these tumours form an infiltrating tumour mass with very poorly differentiated morphology. The cells have very little cytoplasm, the nuclei are hyperchromatic, necrosis is prominent and mitoses obvious. These tumours do stain with neuroendocrine markers, but much less strongly and reliably. Ki-67 can highlight up to 100% of the cells. These poorly differentiated NET are also what have been previously called small cell carcinoma. Although these tumours fall onto a spectrum with the well differentiated NET there are very few examples of tumours that sit in the middle of the range. There are however occasional well differentiated NET with a higher than expected Ki-67 index, that can fall into the grade 3 category, usually reserved for tumours of the poorly differentiated/small cell type.

There are occasional tumours which may have mixed exocrine-endocrine features, usually there is an obvious adenocarcinoma, which focally has areas which resemble a NET and will stain appropriately. These should generally be managed as a standard adenocarcinoma. This problem is compounded in the appendix, where goblet cell carcinoids (GCCs) occur, as these tumours also show both endocrine and adenocarcinomatous differentiation, to varying degrees. Tang has sub-classified GCC into three distinct types, with different prognoses [21].

In the lung, although much of the work on grading NET was done in this area, the terms carcinoid, atypical carcinoid and small cell carcinoma are still used. The carcinoid of the lung looks morphologically similar to that in the GI tract, with a similar immunophenotype. The differentiation from an atypical carcinoid is the presence of >2 mitoses per 10 high power fields, nuclear pleomorphism and necrosis. Similarly small cell carcinoma has the same diagnostic features as in the GI tract.

## 38.6 Clinical Presentation

Local symptoms are dependent on the site of the tumour. For example, patients with NET originating in the gastrointestinal tract may have symptoms including dysphagia, haematemesis, bowel obstruction or obstructive jaundice. Likewise pulmonary NET may result in dyspnoea, haemoptysis, cough and lobar collapse. Some small, non-functional tumours may be found coincidentally. However, functional NET secrete peptides which can result in the development of carcinoid syndrome. This is usually due to metastases in the liver releasing serotonin and tachykinins into the systemic circulation. Typical symptoms consist of flushing, palpitations, diarrhoea and abdominal pain [22]. In severe cases, and sometimes precipitated by anaesthetic induction, it may lead to a carcinoid crisis with life threatening bronchospasm, tachycardia and haemodynamic instability. Patients are managed by high dose octreotide and aggressive fluid resuscitation. One out of every five patients at diagnosis may develop carcinoid heart disease from endocardial thickening of the right-sided chambers. Restriction of the tricuspid and pulmonary valves commonly cause right-sided valvular defects [15, 23].

Functional GEP-NET may arise from the various endocrine glands in the digestive tract and include insulinomas, gastrinomas, VIPomas, glucagonomas, and somatostatinomas. Thus, corresponding symptoms will result from over secretion of the respective peptides. Patients with an insulinoma typically present with symptoms of low blood sugar. Zollinger-Ellison syndrome results from oversecretion of gastrin causing peptic ulcers, abdominal pain and diarrhoea [16]. VIPomas cause watery diarrhoea, hypokalaemia and dehydration. Glucagonomas may result in the development of diabetes mellitus, diarrhoea, venous thrombosis, and neuropsychiatric symptoms. Classical dermatological changes include necrolytic migratory erythema (NME) and cheilitis [24]. Somatostatinomas may cause diabetes mellitus, cholelithiasis and steatorrhea. Constitutional symptoms include anorexia, weight loss and lethargy.

## 38.7 Prognosis

Prognosis may vary depending on a number of factors including site of origin, stage at diagnosis and pathological grading. The 5 year survival of all patients with NET remained at 60–65% between 1973 and 2002. The highest 5 year survival rate of 74–88% was seen in those with rectal primaries and lowest for pancreatic primaries at 27–43%. The typical 5 year survival for patients with locally advanced poorly differentiated NET was 38% and 4% with metastatic disease. Conversely, for patients with well differentiated disease the figures are 82% and 35% respectively [1, 2]. Thus having a primary pancreatic tumour with poorly differentiated histology and extra-hepatic metastases were considered to be negative prognostic factors [25]

## 38.8 Diagnosis

Diagnosis is based on clinical history, measurement of biochemical markers, imaging and histological confirmation.

### 38.8.1 Biochemical Markers

Chromogranin A is present in chromaffin granules of neuroendocrine cells and is usually raised in NET. Concentration correlates with tumour burden [26]. 5-Hydroxyindoleacetic acid (5-HIAA), the main **metabolite** of **serotonin** is the breakdown product of serotonin and may be detected in urine. Measurement of HIAA may achieve a sensitivity and specificity of 73% and 100% respectively [27]. Furthermore, depending on the specific origin of the NET, correlating biochemical markers may be detected (Table 38.2).

**Table 38.2** Specific NET and associated biochemical markers

Subtype	Raised biochemical markers
Insulinoma	Chromogranin A, insulin, blood glucose C peptide, pro-insulin
Gastrinoma	Gastrin
Glucagonoma	Glucagon, enteroglucagon
VIPoma	VIP
Somatostatinoma	SOM
Pancreatic polypeptidoma	Pancreatic polypeptide
MEN 1	Chromogranin A, insulin, glucagon, pancreatic polypeptide

### 38.8.2 *Imaging*

For localization of the primary tumour and staging purposes multimodality imaging including the use of CT, MRI, endoscopic ultrasound, somatostatin receptor scintigraphy (SSRS) and positron emission tomography (PET) may be employed [15]. SSRS involves the intravenous injection of radiolabelled somatostatin analogue. Gallium-68 labelled octreotide PET may assist the detection of tumours not apparent on conventional CT [28]. Iodine-131-labelled metaiodobenzylguanidine (<sup>131</sup>I-MIBG) scintigraphy is useful for identifying tumour uptake and may also be used for therapeutic purposes.

## 38.9 Treatment

### 38.9.1 *Surgery*

Radical resection in localized NET is the only curative approach in patients with NET. Patients may undergo elective resection but occasionally those with bowel NET may present with acute bowel obstruction requiring emergency resection.

### 38.9.2 *Medical Therapy*

Traditionally, interferon alpha (IFN $\alpha$ ) therapy has been used. It activates T-lymphocytes and causes apoptosis. In patients with functional NET, improvement of symptoms due to hormonal hypersecretion and tumour response of around 10% have been reported [29–31]. However, a range of associated toxicities such as fatigue, headache, myalgia and depression mean that long term use may not be tolerated and its use has become less common place in current management.

Known subtypes of somatostatin receptors are SST1, SST2a, SST2b, SST3, SST4 and SST5. Somatostatin analogues include [octreotide](#) and lanreotide are commonly used, but newer generation analogues like pasireotide block a wider range of these [G protein-coupled transmembrane receptors](#). Treatment leads to the down regulation of peptide secretion in functional tumours thus providing symptomatic improvement. Beyond its functional ability, evidence from the PROMID trial suggested an anti-proliferative effect. 85 patients with locally inoperable or metastatic well differentiated midgut tumors were randomized to octreotide or placebo [32]. The median time to tumour progression was found to be significantly longer with octreotide compared to placebo (14.3 vs 6 months). Benefit was seen in both functional as well as non-functional tumours. CLARINET (Lanreotide Antiproliferative Response in patients with GEP-NET) was a large phase III randomised controlled trial assessing the effect of lanreotide on progression free survival (PFS) in non-functioning well to moderately differentiated NET. In the treated group, a significant extension of PFS was reported (HR 0.47;  $p = 0.0002$ ) [33]. Side effects included pain at the injection site, anorexia, nausea, diarrhoea, lethargy and hypoglycaemia.

### 38.9.3 Arterial Embolisation

Systemic radionuclide therapy with  $^{131}\text{I}$ -MIBG is useful as a therapeutic adjunct in managing diffuse metastases demonstrating tracer uptake. Biochemical and radiological response rates reaching 40–60% and 10–15% respectively have been reported [34, 35]. However, repeated use may increase the risk of radiation nephritis, pancytopenia and myelodysplasia

In patients with liver-only metastases, hepatic arterial embolization may be used alone or with infusional chemotherapy. Radioactive microspheres like yttrium-90 injected into tumour sites deliver a high concentration of therapeutic radiation with a sharp fall off which minimizes damage to normal tissue. Percutaneous radiofrequency ablation (RFA) under radiological guidance employs rapidly alternating electric current which generate heat leading to tumour necrosis at the target site.

### 38.9.4 Chemotherapy

One of the earliest trials using chemotherapy was in the 1980s showing modest tumour activity. A randomised controlled study compared 5-fluorouracil (5FU) combined with streptozocin versus doxorubicin showing similar response rates of 22% and 21%. However, this did not translate to any survival benefit [36]. In 1992, a randomised trial using streptozocin combined with [doxorubicin](#) reported a combined biochemical and radiological response rate of 69% and a median survival of 26 months [37]. Follow-up investigation in 2004 compared this two drug combination with the addition of [5-fluorouracil](#) vs triple combination with

streptozocin/5-fluorouracil/ cisplatin. Radiological response rate was reported at 36%, 39% and 38% respectively rate with a median overall survival of 24, 37 and 32 months respectively [38].

Studies investigating capecitabine monotherapy, taxanes, [topotecan](#), and [gemcitabine](#) have yielded response rates of between 0 to 10% [39–43].

Temozolamide has been used in together with other drugs with varying success. Combination of temozolamide with anti-angiogenic drugs like thalidomide and bevacizumab have reported overall response rates of 24–45% [44, 45]. Addition of capecitabine, an oral anti-metabolite, however achieved a response rate of 70% in a very small study [46]. Variation of tumour sensitivity to this alkylating agent could be due to the mediating effect of methylguanine DNA methyltransferase (MGMT). It is postulated that the varied expression of this regulatory protein could account for the effectiveness of the drug, and the absence of MGMT may explain the sensitivity of some tumours [47].

Combination of platinum with a topoisomerase inhibitor has shown some activity. Firstline treatment with [carboplatin](#) plus [etoposide](#) versus [cisplatin](#) plus etoposide demonstrated equivalent response rates of 30% vs 31%, and overall survival of 11 vs 12 months respectively [48]. However, it is postulated that tumours with Ki-67 of <55% were less likely to respond to platinum based chemotherapy regimens [49].

## **38.9.5 Biological Targeted Therapy**

### **38.9.5.1 Tyrosine Kinase Inhibitors**

Tyrosine kinase inhibitors (TKI) are small molecules which disrupt intracellular signalling involved in tumour growth, differentiation and progression. Sunitinib malate is a TKI with activity to receptors including VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptors (PDGFR- $\alpha$  and PDGFR- $\beta$ ). An initial phase II trial of 107 patients with progressive advanced NET used sunitinib at 50 mg o.d. every 4 weeks of a six-weekly cycle [50]. 17% PR was achieved in the PNET and 2% (1/41) of the carcinoid cases. Tumour stabilisation was seen in 68% and 83% respectively after a median follow up of 13.4 months. Median time to progression (TTP) was 7.7 months for PNET and 10.2 months for carcinoid tumours.

Follow up study in a multi-centre randomised, double-blinded placebo-controlled phase III trial for progressive PNET compared the same regimen for sunitinib at 37.5 mg o.d. to placebo [51]. Patients were treated until progression and crossing over to active treatment was allowed after unblinding. Due to significantly more deaths occurring in the placebo group, the trial was terminated. After a median 4.6 months of treatment in 154 evaluable patients, PFS in the treated group was more than double of that in the placebo group at 11.4 months vs 5.5 months (HR 0.42; 95% CI: 0.26 – 0.66;  $p < 0.001$ ).

Response based on RECIST was only seen in the sunitinib patients (9.3% vs 0%) including 2 CR and 6 PR. Benefit was seen irrespective of age, ECOG perfor-

mance status (0, 1 or 2), tumour bulk or history of previous treatment including surgery, chemoembolisation, radiofrequency ablation and somatostatin analogue therapy. The greatest improvement was however found in low grade tumours with Ki-67 of  $\leq 5\%$ .

Side-effects included diarrhoea (59%), nausea (45%), neutropaenia (12% vs 0%) and hypertension (10% vs 0%).

### 38.9.5.2 mTOR Inhibition

Another intracellular pathway of interest involves mTOR (mammalian target of rapamycin) which regulates the PI3K-PIP3-AKT/PKB axis. A series of trials with mTOR inhibitor everolimus led to accumulating evidence for its use, especially in well to moderately differentiated NET. The pilot study with 60 patients assessed dosing the drug at 5 mg o.d versus 10 mg o.d. with octreotide LAR 30 mg every 28 days in progressive carcinoid and PNET [52]. PR rate of 22% was achieved overall, but was higher in the carcinoid compared to the PNET group, and in patients allocated the higher dose (30% vs 13%).

The encouraging results led to the adoption of the 10 mg o.d. dose in the standard arm in an expansion study RADIANT 1 study focusing on patients with progressive PNET [53]. The investigators evaluated the impact of concurrent octreotide therapy and found that the addition of octreotide did not improve the PR rate (9.6% vs 4.4% in favour of the mTOR alone subgroup). However, simultaneous use of octreotide extended PFS better PFS (median 9.7 vs 16.7 months) after a follow-up period of 16 months.

RADIANT 3 followed as the largest multi-centre randomised, double-blinded placebo-controlled phase III trial in patients with progressive PNET. 410 patients were randomised to best supportive care with everolimus 10 mg o.d. or placebo and treated until progression [54]. Unblinding on progression and cross over to active treatment was allowed. After a median follow-up of 17 months there was a clear difference in PFS primary endpoint in favour of the everolimus group achieving 11 months compared to 4.6 months on placebo with a 65% reduction in risk of progression or death (HR 0.35; 95% CI: 0.27- 0.45;  $p < 0.001$ ).

As with TKI treatment, benefit was irrespective of age, clinical performance status, prior treatment or tumour grade (well vs moderately differentiated).

Better tumour response (PR 5% vs 2%), albeit low, and disease stabilisation (73% vs 51%) were possible. This was at a cost of increased grade  $\frac{3}{4}$  side effects including stomatitis (7% vs 0%), anaemia (6% vs 0%), and hyperglycaemia (5% vs 2%) [55].

RADIANT-2 addressed the role of everolimus in carcinoid tumour where 429 patients were randomised to receive everolimus or placebo together with octreotide in a double-blinded phase III trial [56]. Similarly PFS in the everolimus arm was better at 16.4 months compared to 11.3 months in the placebo group, with an associated 23% reduction in risk of progression (HR = 0.77; 95% CI: 0.59-1.00). Although it did not meet its statistical endpoint, a 5.5 month improvement in PFS was reported ( $p = 0.0014$ ).



### 38.9.5.3 Role of VEGF Inhibition with Bevacizumab

Bevacizumab is a recombinant humanised monoclonal antibody to VEGF-A. In a phase II trial 44 patients with metastatic carcinoid tumours were randomised to receive octreotide in combination with 3-weekly bevacizumab at 15 mg/kg or weekly pegylated interferon  $\alpha$ -2b (PIF) at 0.5 mcg/kg [57]. All patients then received all three drugs after a pre-determined 18 week time point. Better partial response (PR) and disease stabilisation rates of 18% vs 0% and 77% vs 68% respectively were seen in the group that started with bevacizumab. Lower rates of progression (5% vs 27%) were also seen and PFS at 18 weeks was also higher (95% vs 68%,  $p=0.02$ ).

Novel surrogate markers for tumour response including tumour blood flow, tumour blood volume and permeability using functional CT were also evaluated. Correspondingly, the bevacizumab group reported a significant reduction in tumour blood flow and blood volume (49% vs 28%, 34% vs 24% respectively).

The combination of everolimus and bevacizumab was evaluated in 39 patients using similar techniques [58]. Patients were treated with either everolimus or bevacizumab for one cycle before a combination of both. The group initiated on bevacizumab reported a 32% decrease in blood flow and those on everolimus resulted in a 13% increase in mean blood transit time. When treatments were combined, synergy was seen with demonstration of further decrease in blood flow and increase in mean transit time was seen, leading to an overall 26% PR and 69% stabilisation rate of 26% and median PFS of 14.4 months.

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# Chapter 39

## Primary Brain Tumors in Adults



**Fernando Silva Picon, Adrialdo José Santos, Hakaru Tadokoro,  
and Ramon Andrade De Mello**

**Abstract** Primary Tumors of the Central Nervous System (PTCNS) are a very heterogeneous group of tumors, which include different types of histology. Their symptoms are variable, according with the local of invasion, compression of adjacent structures, histology and presence of increased intracranial pressure.

**Keywords** GBM · Temozolamide · Radiotherapy

### 39.1 Introduction

Primary Tumors of the Central Nervous System (PTCNS) are a very heterogeneous group of tumors, which include different types of histology. Their symptoms are variable, according with the local of invasion, compression of adjacent structures, histology and presence of increased intracranial pressure.

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## 39.2 Epidemiology

PTCNS are relatively rare tumors. In 2012, the incidence of new cases was about 256,000, which corresponds to 1.8% of all malignancies [1]. The estimated number of deaths was approximately 190,000, which represents 2.3% of all cancer deaths [1].

In the pediatric age group, primary brain tumors are more common and low-grade gliomas are the most frequent. On the other hand, metastases are the most common cause of lesions in the brain parenchyma in the elderly. In this population, high gliomas are more frequent.

Most cases are sporadic, without identifying a causal factor. However, it is known that Neurofibromatosis, von Hippel-Lindau syndrome and Li-Fraumeni syndrome are possibly related to PTCNS [2]. Ionizing radiation is the only environmental factor that has been proven to increase the incidence of these tumors [3]. Otherwise, studies about cell phone use as a risk factor for PTCNS are still controversial [4].

## 39.3 Meningiomas

Meningiomas are the most common PTCNS in the adult population. They are typically extra-axial masses that originate from arachnoid cells of the meningeal. The vast majority are benign. In the most of the cases, the lesions are asymptomatic or minimally symptomatic, which are discovered incidentally. However, depending on the location in the central nervous system, there may be symptoms, like headache and seizures.

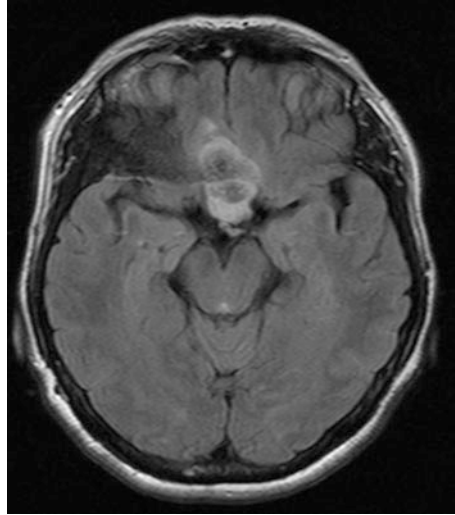
Those tumors are related to aging, being quite uncommon before 65 years of age [5]. Radiotherapy in the head and neurofibromatosis are related to this disease [6]. Epidemiologically, it's know that meningiomas are a little more frequent in women and whites [6].

The World Health Organization (WHO) updated her classification in 2016, which uses morphologic criteria [7].

**WHO Grade I:** those are very well differentiated that do not have any criteria for high risk. The classification includes several morphological subtypes, which are treated in the same way.

**WHO Grade II:** In this new classification, brain invasion is sufficient for the diagnosis of an atypical meningioma. Mitotic activity ( $\geq 4$  mitoses per 10 high potency fields) and characteristic morphological findings are also sufficient for the diagnosis. Additionally, three of the five criteria make the diagnosis: spontaneous necrosis, sheeting (loss of whorling or fascicular architecture), prominent nucleoli, high cellularity and small cells (tumor clusters with high nuclear:cytoplasmic ratio).

**Fig. 39.1** A 56-year-old female presented MRI with an extra-axial expansive lesion of  $4.0 \times 1.9$  cm, with epicenter in the turcica seal, broad dural base and contrast enhancement. There is invasion of the cavernous sinus on the left and the orbit on the right. The optic chiasm is compressed by the tumor, explaining the patient's visual deficit. Images donated by the Department of Oncology of the Universidade Federal de São Paulo



**WHO Grade III:** include anaplastic, papillary, and rhabdoid meningiomas. Anaplastic meningiomas have  $\geq 20$  mitoses per fields or malignant characteristics which resemble carcinoma, sarcoma, or melanoma. Morphologically, there is loss of the meningeal pattern, infiltration of the adjacent brain and necrosis

Magnetic resonance imaging (MRI) is the diagnostic method of choice (Fig. 39.1). Meningiomas are the main cause of extra-axial mass in the CNS, but others possibilities should be remembered like: gliosarcomas, leiomyosarcomas, hemangiopericytomas, neurosarcooidosis or even metastases [8]. Meningiomas also have many somatostatin receptors, making scintigraphy with octreotide an option for the best surgical design [9].

Surgical resection may be curative and is the treatment of choice in symptomatic meningiomas [10]. Commonly, WHO grade I tumors have low growth rate. Therefore, in asymptomatic patients, observation is an option, especially in the elderly population or in individuals with many comorbidities [11]. Brain serial imaging tests are required for follow-up in these cases of expectant conduct.

Patients not candidates for surgery should receive radiotherapy. In a retrospective study with 198 patients [12], radiosurgery and complete resection showed similar progression-free survival (PFS) rate. There were no differences in overall survival and the adverse effects were lower with radiosurgery (10% vs 22%). Radiosurgery was still better in PFS than incomplete resection. These results show that radiotherapy may be an option for non-symptomatic tumors with difficult surgical access and smaller than 3.5 cm.

Patients are stratified for the risk of recurrence for adjuvant radiotherapy [11]. All WHO grade III tumors should receive adjuvant radiotherapy, in the same way as incompletely resected meningioma. Completed resected grade II tumors should be discussed in multidisciplinary teams.

The options for systemic treatment are very meager. For patients with somatostatin positivity in scintigraphy, somatostatin analogs may be an option [13]. Very modest results were found with the use of interferon [14].

## 39.4 Gliomas

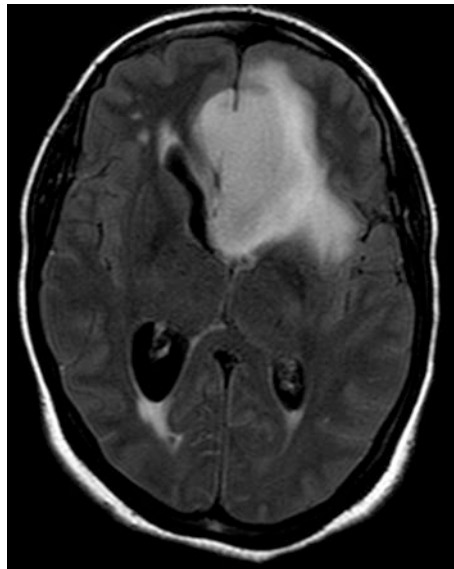
Gliomas are tumors with histological characteristics similar to glial cells, such as astrocytes, oligodendrocytes, and ependymal cells [15]. It is a very heterogeneous group of tumors, with different clinical and prognostic evolution. The disease can occur at all ages, but is more common after the fifth decade of life.

WHO grade I gliomas are more common in pediatric population and generally curable with complete surgical resection. On the other hand, gliomas of WHO grade II or III are invasive and have the ability to progress to higher-grade lesions. WHO grade IV tumors (glioblastomas) are the most invasive form and have a poor prognosis. While the survival of a grade II Oligodendroglioma may exceed 10 years, the median survival of a Glioblastoma is about 15 months [16].

MRI is the best imaging exam (Fig. 39.2), adding several details when compared to CT [11]. The definitive diagnosis is histopathological and biopsy should always be performed when clinical and imaging conditions permit.

The classification has evolved over time. Historically, histological characteristics were used. More recently, the WHO classification has incorporated molecular markers.

**Fig. 39.2** A 33-year-old woman develops severe headache and diminishes strength in the lower right limb. The MRI shows intra-axial expansive lesion of  $8.5 \times 5.0$  cm, with an infiltrative aspect centered on the lower part of the left frontal lobe. Biopsy revealed diffuse astrocytoma (WHO grade II). Images donated by the Department of Oncology of the Universidade Federal de São Paulo





### 39.4.1 Molecular Diagnostic Tests

- (1) **IDH1/IDH2 mutations:** isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* are metabolic enzymes involved in the pathogenesis of malignant gliomas [17]. IDH mutations are commonly associated with codelation of 1p and 19q and have prognostic value. IDH1 and IDH2 mutations have better survival and determines a better sensitivity to radiotherapy and alkylating agents [11].

Those mutations are very common in grade II and III gliomas, but are not found in pilocytic astrocytomas of WHO grade I [17]. In glioblastoma, the mutations are rare, and helps to indicate transformation of low grade lesions in glioblastoma (secondary glioblastoma), which have better prognosis than the primary gliomas [18, 19].

Most IDH1 mutations can be detected by immunohistochemistry. Other IDH1 mutations and IDH2 mutations are only detected by PCR

- (2) **1p/19q codeletion:** Detected by FISH or PCR, the codeletion represents an unbalanced translocation between chromosomes 1 and 19. This is strongly related to oligodendroglial tumors and helps to confirmate the diagnosis [20]. The role in prognosis is also important, since this change is associated with radiosensitivity and better responses with alkylating agents [21]
- (3) **MGMT methylation:** O-6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme naturally found in healthy cells that repairs the damage caused by alkylating agents like temozolomide. Methylation of the promoter *MGMT* gene causes loss of function of this enzyme and greater chemosensitivity to alkylants, with better survival in grade IV gliomas [22].
- (4) **ATRX mutations:** Mutations in the alpha-thalassemia/mental retardation syndrome X-linked (*ATRX*) are related with IDH1/IDH2 mutations. Interestingly, this mutation is mutually exclusive of 1p/19q codeletion. Therefore, the immunohistochemical diagnosis of this mutation favors the diagnosis of the astrocytic lineage and indicates a better survival [23].
- (5) **H3 K27M mutation:** More common in diffuse pediatric gliomas, this mutation can be detected by immunohistochemistry and indicate a worse prognosis [24]

### 39.4.2 Management of Low-grade Glioma

Low-grade gliomas are a group of several distinct entities, with molecular and histopathologic differences [7]. The biologic behavior is also variable, with implications for the treatment and prognosis.

In an analysis of two phase III studies [25], multivariate analysis showed that age > or = 40 years, astrocytoma histology subtype, largest diameter of the tumor > or = 6 cm, tumor crossing the midline, and presence of neurologic deficit before surgery are associated with worse outcomes. Classically, it is believed that

oligodendrogliomas are more delimited, have more calcifications in the imaging tests and have a lower risk of transformation to high grade [26].

Surgery remains the most important strategy for low grade gliomas [27]. In eloquent locations, modern techniques (intraoperative mapping) are useful for reducing sequels [28].

Adjuvant radiotherapy may be useful to increase disease control. There is controversy regarding immediate RT versus progression, since this strategy did not prove an increase in overall survival [29]. However, in high-risk patients, the preference has been for immediate radiotherapy. The preferred doses for RT have been 45–54 Gy [29], since protocols with higher doses have not shown an increase in efficacy [30, 31].

There are no clear recommendations for adjuvant chemotherapy. The RTOG 9802 trial [32], 251 patients with a supratentorial low-grade glioma were randomly assigned to postoperative RT with or without six cycles of adjuvant PCV (procarbazine, lomustine, and vincristine). With a median follow-up time of 11.9 years, there was an increase in overall survival (13.3 versus 7.8 years) with statistical significance. Median progression-free survival was also better in chemotherapy arm PCV (10.4 versus 4.0 years,  $p = 0.002$ ).

Evidence for the use of temozolomide concomitant with radiotherapy is still scarce in the literature. In the phase 2 study RTOG 0424, 129 patients with three or more risk factors for recurrence (age  $\geq 40$  years, astrocytoma histology, bihemispherical tumor, preoperative tumor diameter of  $\geq 6$  cm, or a preoperative neurological dysfunction), were treated with adjuvant radiotherapy (54 Gy in 30 fractions) and concurrent and adjuvant temozolomide. After a medium follow-up of 4.1 years, the three-year progression-free survival was 59.2% and median survival time has not been reached. Compared with historical controls, the authors found benefits in overall survival and recurrence-free survival [33]. Randomized phase III studies are still needed to confirm the benefit of this strategy.

For recurrences, the options are quite limited. Patients should be evaluated for the possibility of surgery or re-treatment with radiotherapy. For systemic treatment, the options are restricted and most authors suggest schemes based on recurrences of high-grade gliomas.

### **39.4.3 Management of High-Grade Glioma**

The treatment is complex and should be discussed in multidisciplinary teams, preferably with radiologist, neuropathologist, neurosurgeons, oncologists and radiation oncologists [16]. Special attention should be given to the clinical management of these patients. In the presence of intracranial hypertension, corticosteroids should be started promptly. The preference is for dexamethasone in the dose of 12–16 mg/day. Management of seizures is also mandatory. Modern non-inducing hepatic agents (lamotrigine, levetiracetam, or valproic acid) are the current preference of neurologists due to lesser interaction with chemotherapy. There is no evidence for

the prophylactic use of corticosteroids or for anticonvulsant medications in asymptomatic patients [11, 16]. Given that they are not free from adverse effects, corticosteroids should be discontinued whenever possible.

Surgery is usually the initial treatment for maximum tumor reduction or at least for biopsy. An aggressive surgical resection has an important prognostic role [34], but due to the infiltrative nature of high-grade gliomas, recurrences are very common.

Radiotherapy (60 Gy, 30–33 fractions of 1.8–2 Gy) has been the standard for adjuvant therapy for high grade gliomas [35]. For elderly or compromised performance status patients, hypofractionated radiation therapy is an acceptable option. In a phase III study, patients older than 70 years were randomized to radiotherapy or only supportive care [36]. The trial was discontinued at the first interim analysis due to the superiority in all analyzed variables (overall survival; progression-free survival, toxicity and health-related quality of life).

A classic phase III study [37] randomized 473 patients with glioblastoma to receive radiotherapy alone or radiotherapy plus continuous daily temozolomide (75 mg per square meter of body-surface area from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150–200 mg per square meter for 5 days for each 28-day cycle). There were benefits in overall survival, with a two-year survival of 26.5% with radiotherapy plus temozolomide and 10.4% with radiotherapy alone. The update of the study after 5 years confirmed the benefit in overall survival [38]. With great clinical importance, MGMT mutations guarantee better response and survival for these patients [22].

WHO Grade III tumors have a better prognosis compared with glioblastoma. Studies with follow-up of more than 10 years [39, 40] demonstrated the role of adjuvant radiotherapy followed by procarbazine, lomustine and vincristine (PCV protocol) in anaplastic oligoastrocytoma and oligodendroglioma recently diagnosed. With a median follow-up of 140 months, the EORTC 26951 study [39] showed significantly benefits in overall survival (42.3 vs 30.6 months in the RT arm) and the 1p/19q-codeleted tumors derive even more benefits. Studies with temozolomide for these patient subgroups are still required.

Distinguishing a progression from a pseudoprogression by MRI can be a challenge in many cases. Pseudoprogression is a subacute treatment-related effect that can occur in about 50% of cases [41]. The presence of clinical deterioration and modern techniques of imaging (spectroscopy and tumor perfusion) may help in diagnostic differentiation [42].

The options for recurrences are quite poor and there is no standard therapy in this setting. The antiangiogenic agent bevacizumab was tested alone or in combination with irinotecan [43, 44]. Although there was some enthusiasm with the response rates in the imaging exams, the survival benefits remain unknown. Other options include: lomustine, PCV, temozolomide rechallenge, re-operation (if feasible), or alternating electric field [11, 16]. Management of symptoms and supportive clinical care should always be taken in this context of severe and advanced disease

## 39.5 Ependymomas

The ependymomas are a very uncommon disease, which represents 2% of all adult CNS tumors [45]. The cerebral ventricular system with ependymal epithelium is the anatomical site, including the vestigial central canal of spinal cord [15]. Didactically they are divided into: supratentorial, infratentorial (posterior fossa) and spinal regions [46].

In adults, tumors in spinal regions are the most frequent, which differs from the pediatric population [46]. There is a clear association between ependymomas of the marrow and type two neurofibromatosis [15].

The intracranial hypertension, and hydrocephalus may be a typical presentation. Signs of focal neurological impairment are seen in supratentorial regions and point to involvement of the cerebral parenchyma.

Case series demonstrate the central role of surgery in this rare neoplasia. The most important prognostic factors are: age, extent of surgery and histology. Grade I ependymomas (subependymomas and myxopapillary) have a greater chance of cure. Supratentorial lesions have a worse prognosis because they have a higher histological grade and greater surgical difficulty [47].

Postoperative radiation therapy increases the recurrence-free survival of patients with intracranial ependymomas [48]. The role of prophylactic spinal irradiation in localized intracranial ependymoma is still controversial. Authors demonstrated that most of the relapses will be local, with no benefits in recurrences on the neuroaxis [49]. However, patients with neuroaxis spread, seen either by MRI or CSF, should receive craniospinal irradiation with boosts on the primary tumor and implants.

There is no evidence for systemic treatment. Some protocols were studied in the pediatric population (carboplatin, etoposide, lomustine), but with disappointing results [11, 46].

## 39.6 Medulloblastoma (MB) and Embryonic Tumor of the Cerebellum (ETC)

This disease group is the most common neoplasia of the brain in childhood. The estimated incidence of new cases of MB and ETC is 1.5 and 0.62 per million population in the USA, respectively [50]. This group of neoplasms is much rarer in adults, with an incidence that is one tenth of that in children. They are classified according to the anatomical location: infratentorial (medulloblastoma) and supratentorial (neuroblastoma and pinealoblastoma).

Medulloblastomas are small cellular tumors with increased cellularity presumed to arise from neuronal precursors in the cerebellum. The presence of anaplasia is a marker of worse prognosis [51]. Due to their characteristic aggressiveness, all PNETS receive WHO classification IV [7].

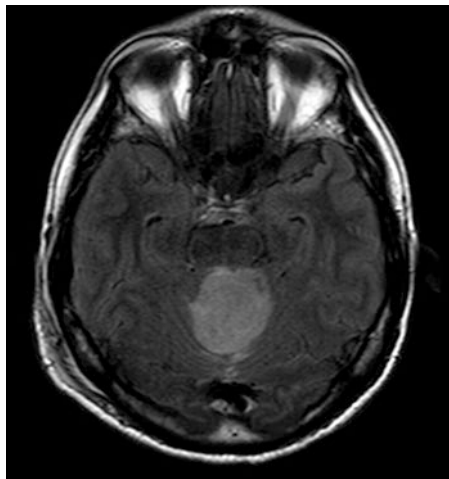
The typical clinical presentation is intracranial hypertension (nocturnal or morning headaches, nausea, vomiting, and mental confusion). As almost all neuroblastomas occur in the cerebellum, ataxias and incoordination can be seen in this disease. In medulloblastomas, the most common finding of MRI is a mass in the cerebellar region with compression of the IV ventricle [52] (Fig. 39.3). Dissemination via cerebrospinal fluid is not uncommon.

Surgery is the initial treatment of choice. It has role in obtaining tissue for histological diagnosis, in the treatment of intracranial hypertension, symptom relief and local control [53].

Based on studies in the pediatric population, there is a consensus that adjuvant radiotherapy should always be offered. The usual dose is 36 Gy to the entire craniospinal axis and 55 Gy to the posterior fossa. In a retrospective analysis of 32 patients, overall survival rates at 5 and 8 years were 83 and 45% and disease-free survival rates were 57 and 40%, respectively. Twenty patients from this study had chemotherapy before radiotherapy and another four after [54].

For average-risk medulloblastoma, the current trend is for radiation dose reduction protocols. Two studies evaluated 23.4 Gy in the craniospinal irradiation, but maintaining 55.8 Gy in the primary site. Radiotherapy was started 28 days after surgery with high-dose chemotherapy protocols with cyclophosphamide, cisplatin, and vincristine, with or without bone marrow or stem cell support. Those studies demonstrated that dose reduction did not decrease disease control [55, 56].

Another strategy to decrease the dose of radiotherapy in the neuro-axis is adjuvant chemotherapy. In an important phase III study of 421 patients 3–21 years of



**Fig. 39.3** A 44-year-old man begins severe headache, nausea and vomiting. MRI shows a  $3.9 \times 3.0 \times 2.5$  cm lesion in cerebellar topography, which shows intense contrast enhancement and signs of diffusion restriction of water molecules. There is compression of the IV ventricle, the cerebellar parenchyma and structures of the brainstem. The biopsy showed a classic medulloblastoma (WHO grade IV.). Images donated by the Department of Oncology of the Universidade Federal de São Paulo

age with intermediate-risk medulloblastoma, vincristine was given during radiotherapy, followed by eight adjuvant cycles of platinum-based chemotherapy. The results were very encouraging, with recurrence-free and overall five-year survival of 81% and 86%, respectively [57].

For recurrences, the evidence is very limited. Based on phase II studies, there are options for high dose chemotherapy with autologous stem cell support and temozolomide [58–60].

## 39.7 Primary CNS Lymphomas

Primary central nervous system lymphoma (PCNSL) is an aggressive type of non-Hodgkin's lymphoma that can affect brain, eyes, leptomeninges, or spinal cord without evidence of systemic disease. The disease is rare, accounting for about 4% of all CNS neoplasms [61]. Immunosuppression is the main risk factor for PCNSL and the increase in its occurrence in the last decades can be explained by the AIDS epidemic and the increase in transplanted patients [61].

The tumor has infiltrative characteristics, being not uncommon the multifocal presentation. Therefore, the symptoms are quite variable and correlate with anatomical position, infiltration or not of leptomeninges and involvement of cranial nerves. In more than 90% of cases, the characteristic phenotype is B lymphoma [62].

The surgery has paper only for tissue samples for biopsy. Extensive surgeries have already been related to poor prognosis. PCNSL has high sensitivity to corticosteroids, which can be used for symptomatic relief. However, they should not be used prophylactically in asymptomatic patients, since tumor regression may hinder the biopsy [11].

Methotrexate is the most active chemotherapeutic agent and treatment protocols use it alone or in combinations with other chemotherapeutic agents [63, 64]. The rituximab addition could add additional benefit and is well tolerated [65]. Anti-retroviral therapy has proved advantageous in HIV-positive patients with low CD4 counts [66]. Adjuvant radiotherapy was used as standard adjuvant treatment. However, more recent studies have shown safety in delaying its use for progression, which could decrease toxicities. Therefore, if there is a satisfactory response to systemic treatment, radiotherapy may or may not be indicated.

### Primary Brain Tumors in Adults – Questions

- (1) **Based on the epidemiology of Primary Tumors of the Central Nervous System (PTCNS), it is possible to state that:**
  - (a) In the pediatric population, the most common cause of CNS tumors are metastases, as well as in the adult population
  - (b) High-grade gliomas are the most common type of glioma in children
  - (c) Primary Tumors of the Central Nervous System (PTCNS) are a very heterogeneous group of tumors, which include different types of histology.

- (d) In adults, we expect a higher incidence of low grade gliomas than high grade gliomas
- (2) **About the PTCNS, mark the only alternative INCORRECT:**
- (a) Neurofibromatosis, von Hippel-Lindau syndrome and Li-Fraumeni syndrome are genetic syndromes possibly related to PTCNS
  - (b) Ionizing radiation is the only environmental factor that has been proven to increase the incidence of these tumors
  - (c) Meningiomas, the most common PTCNS in the adult population, are typically extra-axial masses that originate from arachnoid cells of the meningeal. The vast majority are benign.
  - (d) The vast majority of meningiomas present with persistent headache and compressive symptoms
- (3) **Patient aged 84 years presents with seizures. Image exams demonstrate an extra-axial image of 4 cm that could be the cause of the symptoms. Regarding the treatment of this patient, it is INCORRECT to state:**
- (a) Meningiomas are the main cause of extra-axial mass in the CNS, but others possibilities should be remembered like: gliosarcomas, leiomyosarcomas, hemangiopericytomas, neurosarcooidosis or even metastases.
  - (b) Recent advances in radiotherapy have made surgery unnecessary. The best option for this patient would be radiotherapy.
  - (c) Options for systemic treatment are very scarce. Options include octreotide for patients who are positive for somatostatin receptors in scintigraphy or interferon.
  - (d) Radiotherapy is a strategy for adjuvant in non-fully resected symptomatic tumors and also for high-grade diseases.
- (4) **Taking into account the previous case, it ISN'T POSSIBLE to affirm:**
- (a) Surgery is curative treatment of this disease.
  - (b) The presence of residual disease is a prognostic factor.
  - (c) Incidental findings in patients who are very old or have a lot of comorbidities may only be followed as long as they are asymptomatic.
  - (d) In patients not candidates for surgery, radiotherapy was not superior to observation in large and symptomatic lesions
- (5) **Regarding gliomas in adults, it is possible to affirm:**
- (a) Glioblastoma is the most common subtype in this population.
  - (b) Adult gliomas are a group of very similar diseases, which explains the similar prognosis of different classes
  - (c) Most glioblastomas come from low grade diseases that progress.
  - (d) Grade I gliomas are much more common in adults than in children

- (6) **Genetic markers were a major breakthrough in understanding gliomas. For this reason, they were incorporated into the most recent classification of this disease. Regarding these genetic markers, mark the correct alternative:**
- (a) IDH1 and IDH2 and the codelation of 1p and 19q are mutually exclusive genetic alterations. Therefore, if a patient presents the first one, he will not have the codelation.
  - (b) IDH1 and IDH2 mutations are diagnosed only by advanced PCR techniques
  - (c) The unbalanced translocation between chromosomes 1 and 19, diagnosed by PCR or FISH, is a marker of the astrocytic lineage, aiding in the diagnosis of this subtype.
  - (d) IDH1 / IDH2 mutations and 1p/19q codeletion correlate with better prognosis and greater sensitivity to radiotherapy.
- (7) **Regarding low-grade gliomas, it is incorrect to say:**
- (a) Age  $>$  or  $=$  40 years, astrocytoma histology subtype, largest diameter of the tumor  $>$  or  $=$  6 cm, tumor crossing the midline, and presence of neurologic deficit before surgery are associated with worse outcomes
  - (b) In high-risk patients, the preference has been for immediate radiotherapy. The preferred doses for RT have been 45–54 Gy, since protocols with higher doses have not shown an increase in efficacy.
  - (c) The RTOG 9802 trial showed no increase in overall survival with six cycles of adjuvant PCV.
  - (d) Adjuvant radiotherapy increases the disease control, but there is controversy in overall survival.
- (8) **On molecular diagnoses, check the one that is most frequent in glioblastoma:**
- (a) IDH1/IDH2 mutations
  - (b) 1p/19q codeletion
  - (c) H3 K27M mutation
  - (d) MGMT methylation
- (9) **Which of the molecular marker markers is most commonly found in the pediatric population:**
- (a) H3 K27M mutation
  - (b) ATRX mutations
  - (c) 1p/19q codeletion
  - (d) MGMT methylation
- (10) **High-grade gliomas are diseases of poor prognosis. Regarding this condition, it is correct to say:**



- (a) Seizures are a frequent complication of this disease. Prophylactic use of anticonvulsants is a useful strategy and should be used in clinical practice.
  - (b) Glioblastomas are well localized diseases and surgery may be sufficient for the cure.
  - (c) Mutation of MGMT has prognostic value, being associated with greater sensitivity to chemotherapy with alkylating agents.
  - (d) A phase III study conducted by Stupp et al demonstrated the role of the adjuvant PCV regimen in glioblastoma, being the standard in most centers.
- (11) **A healthy 88-year-old patient is admitted to the emergency department with recurrent seizures. An MRI showed an expansive image in the parietal lobe with infiltrative characteristics. Regarding the case, it is correct to say:**
- (a) By age and characteristics, metastasis is not a possibility.
  - (b) Contrast cranial tomography is the best examination in these situations and helps in the differentiation of secondary neoplasms.
  - (c) Since prophylaxis with anticonvulsant drugs is not a consensus, this patient should not receive them.
  - (d) As the patient is healthy and functional, a guided biopsy should be proposed for patient and family
- (12) **The patient of the previous question underwent a biopsy and the result of was a glioblastoma. Patient is clinically stable with Karnofsky score of 90. On this case, what is the INCORRECT conduct?**
- (a) Maximal resection of the lesion has a prognostic impact and should be attempted.
  - (b) For elderly patients or for patients with poor clinical performance, adjuvant radiotherapy without concomitant chemotherapy is an acceptable option.
  - (c) Prophylactic use of corticosteroids prevents radiation-induced cranial hypertension.
  - (d) A phase III study comparing the addition of temozolomide to radiotherapy versus single radiotherapy showed the benefit of chemotherapy.
- (13) **About alternating electric field, it is correct to state:**
- (a) Dermatitis is a frequent complication.
  - (b) It is a revolutionary treatment, used instead of the chemotherapy concomitant with radiotherapy.
  - (c) It demonstrated benefits over PCV scheme.
  - (d) Adverse hematological and gastrointestinal effects are comparable to those induced by chemotherapy
- (14) **Regarding the rare PTCNSs, it is correct to state that:**
- (a) The ependymal epithelium of cerebral ventricular system with is the anatomical site of ependymomas, a very uncommon disease.

- (b) Supratentorial embryonic tumors have a better prognosis than infratentorial.
- (c) Medulloblastoma and Embryonal Tumor of the Cerebellum are diseases related to aging, with the peak incidence at 70 years.
- (d) The treatment of medulloblastoma is surgical, and there is no evidence for adjuvant radiotherapy or chemotherapy.

**(15) Regarding the rare PTCNSs, it is correct to state that:**

- (a) Primary central nervous system lymphoma (PCNSL) is a rare type of Hodgkin lymphoma.
- (b) The increase in the use of immunosuppressors and the AIDS epidemic explain the increase in the incidence of primary central nervous system lymphoma in the last decades.
- (c) Rituximab failed to demonstrate benefit for this disease.
- (d) More recent protocols have abandoned the use of methotrexate and systemic corticosteroids should be avoided.

**Answers**

- 1. (c)
- 2. (d)
- 3. (b)
- 4. (d)
- 5. (a)
- 6. (d)
- 7. (c)
- 8. (d)
- 9. (a)
- 10. (c)
- 11. (d)
- 12. (c)
- 13. (a)
- 14. (a)
- 15. (b)

**Justifications**

- 1. Low-grade gliomas are the most common lesions in pediatric patients. Metastases at this age are very unusual, being the opposite of the geriatric population. Epidemiologically, high-grade gliomas are the most common lesions in adults, especially glioblastoma.
- 2. The incorrect alternative is D, since statistically the majority of meningiomas are asymptomatic.
- 3. Despite the advances in radiotherapy, surgery is still the main treatment of meningiomas. The options for systemic treatment are few. Adjuvant radiotherapy may be proposed in high-risk lesions.
- 4. In patients not candidates for surgery, radiotherapy is an appropriate option for local control of symptomatic lesions. Surgery is the treatment of choice and has healing potential. The presence of residual lesion increases postoperative

relapses and symptoms. Observation in asymptomatic patients is always a viable option.

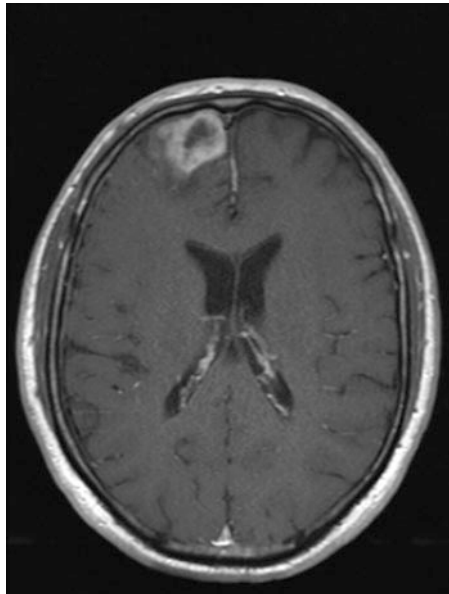
5. Gliomas are a heterogeneous group of diseases, with very different prognoses. Glioblastomas are the most frequent gliomas in the adult population and only a minority comes from low grade lesions that have undergone to progression. Grade I gliomas are a very rare disease, being more often found in children than in adults.
6. IDH1 and IDH2 and the codelation of 1p and 19q aren't mutually exclusive genetic alterations and should be searched separately. IDH1 and IDH2 mutations can be diagnosed by PCR techniques, but also by immunohistochemistry, which is more accessible. On alternative C, the unbalanced translocation between chromosomes 1 and 19 is related to the oligodendroglial lineage and not to astrocytic. The alternative D is the only correct one. The two mutations are associated with better prognosis and better sensitivity to radiotherapy.
7. Alternative A is conceptual and all these factors are related to the best prognosis in the studies. Alternative B is also correct and we must remember that protocols with high doses of radiotherapy did not show benefits when compared with the conventional protocols. The RTOG 9802 trial showed benefits for the PCV scheme including for overall survival. The greatest benefit of radiotherapy seems to be for local control. There are controversies regarding the overall survival benefit.
8. Statistically, MGMT methylation is the most common mutation in glioblastoma.
9. H3 K27M mutation is more common in diffuse pediatric gliomas.
10. There is no evidence for the prophylactic use of anticonvulsant medications. Glioblastoma is an infiltrative and diffuse disease, being these important characteristics of the anatomopathological examination. Mutation of MGMT increases sensitivity to chemotherapy, ensuring a better prognosis. The phase III study conducted by Stup et al used temozolomide and not PCV (Ref. [37]).
11. In the patient's age range, metastasis may be a possibility. The best imaging test for this patient is magnetic resonance imaging (MRI) of the skull and not a CT scan. Alternative C is also incorrect. The patient has recurrent seizures, so it is not a prophylactic use, but a treatment for his condition. Biopsy is the gold standard for diagnosis and should always be attempted if the patient has satisfactory clinical conditions.
12. Maximal resection of the lesion has a prognostic impact and should be attempted whenever the patients have conditions for surgery. Alternative B is also correct. A phase III study comparing radiotherapy with BSC demonstrated benefits for radiotherapy (Ref. [36]). There is no evidence of any measures for the prevention of intracranial hypertension induced by radiotherapy. There is no evidence of any measure for the prevention of intracranial hypertension induced by radiotherapy and therefore the alternative C is the incorrect one. The alternative D provides valid information about an important phase III study on the subject.
13. Alternating electric field is a new treatment. Dermatitis is a possible adverse effect caused by electrode burns (alternative A is correct). There is no evidence

for its use instead of chemotherapy concomitant with radiation therapy. The studies used it in comparison to the chemotherapy on relapse and she had comparable results. One of the advantages of this strategy is the lower incidence of hematological and gastrointestinal adverse effects.

14. Alternative A provides conceptual data and is the correct one. Infratentorial embryonic tumors have a better prognosis than supratentorial ones. Medulloblastoma and Embryonal Tumor of the Cerebellum are diseases of childhood. Radiotherapy and chemotherapy are important in the adjuvant treatment of medulloblastoma.
15. Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma. Alternative B is correct. The increase in immunosuppressed patients, whether through the use of immunosuppressants in transplants or through the spread of the AIDS epidemic, is a possible explanation for the increase in the number of cases of this rare disease. Rituximab can be an option for this disease (Ref. [65]). methotrexate and systemic corticosteroids remain the basis of treatment of this disease

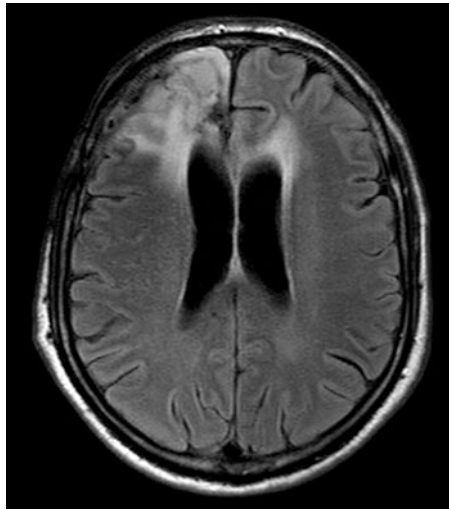
### Clinical Case

A previously healthy 64-year-old man had a generalized tonic-clonic seizure crisis on February of 2016. Patient was submitted to a nuclear magnetic resonance of the brain, which showed: “Extensive and infiltrative frontal corticosubcortical lesion affecting the superior frontal rotations, and frontal-orbital rotations presenting hypersignal in T2 / FLAIR and hyposignal in T1. There is apparent extension to the corpus callosum on the right and contact with ipsilateral frontal horn. There is irregular and moderate contrast enhancement in the corticosubcortical portion. There are foci of diffusion restriction in some cortical portions.”

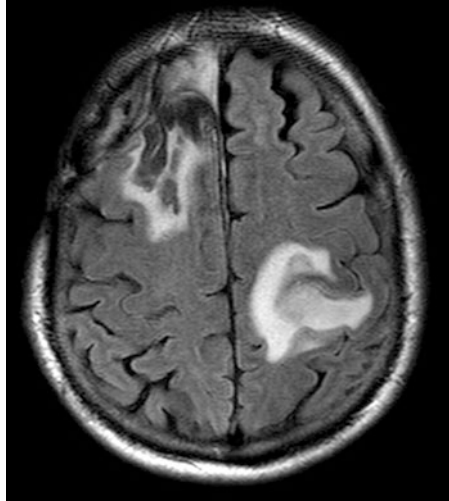


The patient performed a biopsy of the lesion 2 days later. The anatomopathological results were obtained from WHO grade IV glioblastoma. After surgery, the patient began to behave inappropriately, urinating in inappropriate places, opening the taps of the house without closing, resisting for bathing and personal hygiene. Your children have noticed that in the last 4 months they have stopped doing some activities at home that they usually do and lose concentration easily.

The multidisciplinary medical team chose to initiate temozolomide concomitant with radiotherapy, followed by additional cycles of adjuvant temozolomide, following the protocol published by Stupp et al (Ref. [37]). Radiotherapy with a total dose of 60 Gy was initiated in April 2016 with 75 mg of temozolomide per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy. Twelve additional cycles of temozolomide at a dose of 200 mg per square meter were made from July 2016 to July 2017 with good tolerance. The control resonance at the end of treatment is below.



In October 2017, patient presented recurrence of the disease in the left frontal region. There was clinical worsening of the patient and new seizures. The case was discussed at a multidisciplinary meeting and new surgery was ruled out. Second-line chemotherapy with lomustine has been started.



*Images donated by the Department of Oncology of the Universidade Federal de São Paulo.*

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**Part III**  
**Hemato-Oncology**

# Chapter 40

## Acute Lymphoblastic Leukemia



Eddy Supriyadi and Pudjo Hagung Widjanto

**Abstract** Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, accounts for one-fourth of childhood cancers. The incidence peaks in children aged between 2 and 5 years, which is higher in boys than girls. Genetic factors, environmental factors, viral infection, and immunodeficiency have been associated with ALL. However, the cause of ALL remains unknown. ALL may be found on incidental finding on a routine blood cell count of an asymptomatic child or as a life-threatening hemorrhage or infections. The diagnosis is based on clinical findings and laboratory examinations included: leukemic lymphoblasts examination for morphologic, immunologic, cytogenetic and molecular genetics characterizations. The treatment typically consists of four phases: a remission induction, intensification, CNS prophylaxis and continuation therapy, and should be adapted on the local situation. Leukocyte count, age at diagnosis and immunophenotype are important prognostic factors.

**Keywords** ALL · Diagnostic · Treatment · Prognostic

### Abbreviations

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloblastic Leukemia
DNA	Deoxyribonucleic Acid
EFS	Event-Free Survival
CNS	Central Nervous System
WBC	White Blood Cell
GIT	Gastro Intestinal Tract
LDH	Lactate Dehydrogenase

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DIC	Disseminated Intravascular Coagulation
FAB	French American British
WHO	World Health Organization
CD	Cluster of Differentiation
CNS	Central Nervous System
6-MP	6-Mercaptopurine
MTX	Methotrexate
TLS	Tumor Lysis Syndrome

## 40.1 Introduction

Leukemia, a malignant disorder of hematological progenitor cells, is the most frequent type of cancer in children. Acute lymphoblastic leukemia (ALL) is the most common cancer in children under 15 years of age with peak incidence 2–5 years. It is represent about 20% of adult acute leukemias, accounting for 26% of all cancers in this age group [1–3].

## 40.2 Epidemiology

The average incidence of this malignant childhood disease in the European Region was 46.7 cases per million per year in 2000. In France, the reported incidence of ALL was 34.3 and acute myeloblastic leukemia (AML) was 7.1 per million population [4]. In the United States an estimated 2900 children and adolescents younger than 20 years are diagnosed with ALL each year [5].

### 40.2.1 Incidence and Prevalence

Annual incidence of childhood ALL is 3.0–3.5 per 100,000, and it varies among countries, geographic regions and by race and ethnic origin. It is also associated with rural population growth [6–9]. Social mixing of children in young age had an impact of early exposure to infection. It plays a role in the reduced the ALL incidence. In low-income countries such as Indonesia, environmental factors may have a role in the incidence of childhood ALL [10]. Factors that could play a role in the incidence of leukemia are: genetics, radiation, chemical and drugs, infections, socio-economic status and immunological status [11–18].

### 40.3 Molecular Mechanisms

Acute lymphoblastic leukemia is a disease starts in the bone marrow. Normal blood cells population replaced by uncontrolled proliferation of young white blood cells (leukemic cells). Deletions of chromosome, mutations or chemical alterations of DNA may cause inactivation of the tumor suppressor gene or activation of the oncogene. Normal apoptosis (i.e. Bcl-2 pathway) may be disturbed and lead to increase in cellular proliferation also decreasing of cell death.

Genetic studies in leukemia at the time of diagnosis are important with regards to prognostic and the treatment choice [19]. Standard cytogenetic analyses can detect abnormalities in about 75% of ALL cases. The information obtained from genetic studies on lymphoblasts at diagnosis can improve cure rates in childhood leukemia, together with clinical features and initial response to therapy [20, 21]. The most common genetic associated alterations are listed in Table 40.1. These alterations have an estimated Event-Free Survival (EFS) of greater than 80% [22, 23]. Note that these data are derived from studies in western countries, on the genetic alterations in low-income countries in Africa and Asia exists relatively little data (Fig. 40.1).

**Table 40.1** Characteristic and clinical outcomes

Subtype and genetic abnormalities	Frequency (%)	Clinical implication	Estimated 5 years EFS (%)
<b>B-lineage</b>			
Hyperdiploidy >50	20–30	Excellent prognosis with antimetabolite-based therapy	85–95
Hypodiploidy <44	1–2	Poor prognosis	30–40
Trisomies 4 and 10	20–25	Excellent prognosis with antimetabolite-based therapy	85–90
t(12;21)(p13;q22) ETV6-RUNX1 (Formerly known as TEL-AML1)	15–25	Excellent prognosis with intensive Asparaginase therapy	80–95
t(9;22)(q34;q11.2) BCR-ABL1	2–4	Imatinib plus intensive chemotherapy improve early treatment outcome	80–90 at 3 years
t(v;11q23);MLL rearranged t(5;14)(q31;q32) IL3-IGH			
t(1;19)(q23;p13.3);TCF3-PBX1	2–6	Increased incidence in blacks; excellent prognosis with high-dose methotrexate treatment; increased risk of CNS relapse in some studies	80–85
<b>T-Lineage</b>			
MLL-ENL	2–4	Favorable prognosis	80–90

Cited from Pui, 2011 [37]

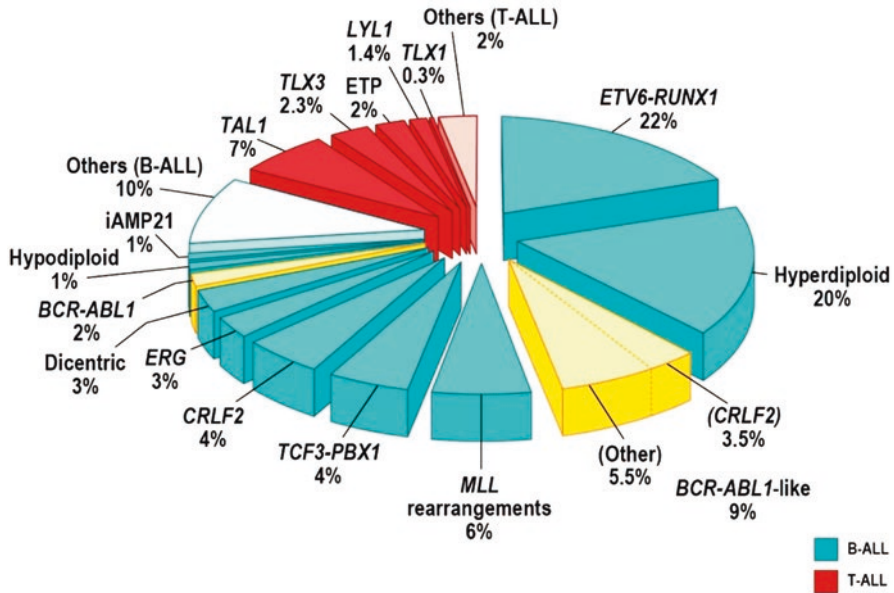


Fig. 40.1 Frequency of cytogenetic subtypes of pediatric ALL [38]. (Cited from Mullighan 2012)

## 40.4 Diagnosis

### 40.4.1 Clinical Manifestation

Symptoms and clinical manifestations reflect of bone marrow infiltration by leukemic cells. Pallor, fever, muscle pain, bone pain, fatigue, bleeding (i.e. gum bleeding, epistaxis, petechiae, purpura, hematemesis and melena). The length of symptoms could be in weeks and occasionally several months. In physical examination: organomegaly can be found. In complete blood count examination: Anemia, bicytopenia and often pancytopenia may be found.

Anemia: reflects of pressed erythropoiesis by young or immature leukocyte. Fever reflects infections due to low immunological status as peripheral blood is dominated by young white blood cells, while white blood cells count: could be low, normal or high. Platelets: The platelets count usually low, and spontaneous bleeding can appear with platelet count 20.000–30.000/dL [24, 25]. Summarized of clinical manifestations are listed in the Table 40.2.

**Table 40.2** Clinical presentation of ALL

<b>The clinical presentation of ALL:</b>	
Sign of anemia	Lethargy, weariness, fatigue, rapid exhaustion, lack of appetite. Laboratory: Normocytic, normochromic anemia
Signs of infections	Febrile illness. Laboratory: reduced of absolute neutrophil count
Signs of bleeding tendency	Purpura, mucosal bleeding, hematomas and bruising. Laboratory: thrombocytopenia, occasional coagulopathy
Signs of organ infiltration	Bone and joint discomfort, hepatomegaly, generalized lymph node swelling, mediastinal mass and subsequent superior vena cava obstruction
Signs of systemic disease	Fever of unknown origin, weight loss, night sweats

Cited from Owen P. Smith and Ian M. Hann Clinical features and therapy of lymphoblastic leukemia

## 40.4.2 *Clinical Manifestations in Other Systems*

### 40.4.2.1 Central Nervous System Manifestations

Involvement of central nervous system (CNS) leukemia is defined by the presence of lymphoblast in the cerebrospinal fluid. It is found in 1.2–10% of children with newly diagnosed ALL. Leukemic blasts entering the CNS by hematogenous spread. CNS leukemia is more common in mature B cell, T-ALL and children with high WBC. Signs of CNS involvement:

- Signs of increased intracranial pressure (headache, papilledema and lethargy)
- Signs and symptoms of parenchymal involvement (e.g., focal neurologic signs such as hemiparesis, cranial nerve palsies, convulsions, cerebellar involvement – ataxia, dysmetria, hypotonia, hyperflexia)
- Cranial nerve involvement: n. III, IV, VI and VII [26, 27].

### 40.4.2.2 Cardiopulmonary Involvement

Leukemic involvement in the lungs and heart is rare. The manifestations could be: pericardial leukemic effusion and mediastinal mass, especially in T-ALL. Late cardiomyopathy is found after extensive treatment with anthracyclines [28].

#### 40.4.2.3 Other Organ Involvement

Mediastinal mass (thymus enlargement) due to leukemic infiltration, may cause life-threatening Especially in T-ALL: superior vena cava syndrome.

In the eye, retinal bleeding caused by high white blood cell count and/or thrombocytopenia.

Involvement of musculoskeletal is characterized by severe pain, especially in lower extremities and sometimes unable or refusal to walk. This symptom occurred in 20–30% of children with ALL. It may result of infiltration of leukemic cells to the bone or expansion marrow cavity by leukemic cells. It may also appear swelling and tenderness due to leukemic infiltration [29, 30]. Involvement of UT testicular is present mostly in boys. Testicular involvement is diagnosed if leukemic blasts found by testicular biopsy. It is occurred only in boys with WBC >25.000/dL, T-cell ALL, moderate to severe hepatosplenomegaly, lymphadenopathy and thrombocytopenia (<30,000/dl). In girls, ovarian involvement occurs very rare [31]. The commonest manifestation of leukemia in GIT is bleeding, as reflected by occult blood in the stool. GIT bleeding might also be caused by thrombocytopenia, DIC or infection. Neutropenic typhilitis or necrotizing enterocolitis diagnosed if right lower quadrant pain with tenderness, abdominal tension, vomiting and sepsis are found.

#### 40.4.2.4 Radiology Changes

Radiology changes are found at metaphysis is transverse radiolucent line, subperiosteal new bone formation and osteolytic lesion involving medullary cavity and cortex.

Diagnostic of ALL is based on clinical findings and some laboratory tests. Basic investigation required for diagnostic ALL are [32–35]:

#### 40.4.3 Blood Tests

Examination of complete blood count, differential blood count including morphology, lactate dehydrogenase (LDH), electrolyte, renal function tests, liver function tests, coagulation screening is necessary. Abnormal liver function test may be due to leukemic infiltration to the liver. Serum chemistry: Uric acid, potassium and calcium may be abnormal due to cell lysis as an impact of high WBC and chemotherapy. Serum lactate dehydrogenase usually high, and it may be has a prognostic value [36–38]. Morphology of leukemic cells can be examined from peripheral blood smear and bone marrow smear, hence morphology of peripheral blood and BM smear is critical. Hemoglobin: Normocytic; normochromic red cells morphology. Low hemoglobin indicates longer duration of leukemia; higher hemoglobin indicates a more rapidly proliferating leukemia. White blood cell (WBC) count can be below, normal, or increased.



Blood smear: lymphoblasts are detected in children with high WBC however very few to none in patients with leukopenia. When WBC is greater than 10,000/dl, blasts are usually abundant. Eosinophilia is occasionally seen in children with ALL; 20% of patients with AML have an increased number of basophils.

Platelet. Thrombocytopenia: 92% of patients have platelet count below normal. Serious hemorrhage (Gastro intestinal tract or intracranial) occurs at platelet counts less than 25,000/dl.

#### **40.4.4 Bone Marrow Tests**

Diagnostic tools may vary among countries. It depends on the ability of each country to provide. The Important thing is morphology both from peripheral blood and bone marrow. Bone-marrow aspiration done under sterile conditions in the posterior iliac region is recommended for diagnosis of acute lymphoblastic leukemia because morphology of leukemic cells in bone marrow can be different from those in peripheral smear and 20% of patients with acute lymphoblastic leukemia do not have circulating blast cells at diagnosis [39]. Site of aspiration is recommended in the posterior iliac region for children above 2 years of age, and for children under 2 years at tibia. Sternal aspiration is contraindicated in young children.

#### **40.4.5 Morphology – FAB Classification**

Leukemia must be suspected when the bone marrow contains more than 5% blasts. The hallmark of the diagnosis of acute leukemia is the blast cells, a relatively undifferentiated cell with diffusely distributed nuclear chromatin, one or more nucleoli, and basophilic cytoplasm. Special bone marrow studies, will help in detailed classification, include the following: Cytochemistry, Immunophenotyping, Cytogenetic and DNA content [33]. Bone marrow smears stained with other May-Grünwald-Giemsa or Wright-Giemsa, and should be examined under a light microscope. It is important to examine the morphology of leukemic cells to distinguish lymphoblast and myeloblast. Acute leukemia can be classified based on morphological characteristics into lymphoblastic leukemia and myeloblastic leukemia (Table 40.3a.).

Cytochemical features are needed to sharpen the diagnosis. Cytochemistry for myeloperoxidase and non-specific esterase should be done to exclude acute myeloblastic leukemia [40]. To support diagnosis of ALL, cytochemistry such as periodic acid shift (PAS), peroxidase and Sudan-Black staining are recommended (Table 40.3b.).

The French-American-British (FAB) Working Group Classification of ALL is based on morphologic and cytochemical features. Peripheral blood and bone marrow smears are stained (May-Grünwald-Giemsa method) and analyzed by light microscopy. Leukemic cells are characterized by a lack of differentiation, by a

**Table 40.3a** Lymphoblast and Myeloblast characteristic

	Lymphoblast	Myeloblast
Cell size	10–20 um	14–20 um
Cytoplasm	Blue, usually homogenous, sometimes with vacuoles	Blue-gray, Granular, sometimes with Auer rods
Nucleus chromatin	Homogenous and or fine	Heterogeneous
Nucleoli	0–2, distinct	2–5 distinct “punched out”
Nucleus/cytoplasm ratio	High	Low

**Table 40.3b** Cytochemistry characteristic of Lymphoblast -Myeloblast

	Lymphoblast	Myeloblast
PAS	++	-/+
Sudan Black	-	+
Peroxidase	-	+
Esterase	-	+/-

**Table 40.4** French-American-British (FAB) classification of lymphoblasts

	L1	L2	L3
Cell size	Small	Variable	Large, heterogeneous
Nuclear shape	Regular, occasionally clefting	Irregular, clefting, indentation common	Regular, oval to round
Chromatin	Homogenous	Variable, heterogeneous	Finely stippled and homogeneous
Nucleoli	Not visible,	Often large, one or more present	Prominent, one or more
Cytoplasm	Scanty	Variable, often moderately abundant	Moderately abundant
Basophilic of cytoplasm	Very view	Variable, sometimes deep	Very deep
Cytoplasmic vacuolization	Variable	Variable	Often prominent

nucleus with diffuse chromatin structure, with one or more nucleoli, and by basophilic cytoplasm. This morphologic classification system categorizes lymphoblastic leukemias into three subtypes: L1 and L2 and L3 (Table 40.4.) [25].

**Table 40.5** WHO classification of acute leukemia

	<b>B-Lineage</b>	<b>T-Lineage</b>	<b>AML</b>
<b>Monoclonal antibody</b>	CD10	CD2	CD13
	CD19	Cytoplasmic CD3	CD33
	CD20	CD5	CD117
	CD22	CD7	Cytoplasmic MPO
	CD34		
	Cytoplasmic CD79a		
	HLA-DR		
	IgM		
	TdT		

#### 40.4.6 Immunophenotyping

Immunophenotyping of abnormal hematological cells using flowcytometry studies on peripheral blood or bone marrow samples, improves both accuracy and reproducibility of classification of acute leukemias [41–46]. It is very useful for the diagnosis, classification, cost-effective treatment and prognostic evaluation in patients with hematological malignancies [47–49]. Usually, ALL is classified into T-lineage, B-lineage, and B-cell (Burkitt’s) phenotypes. The World Health Organization (WHO) classification (Table 40.5.) divides ALL into two main groups only, i.e., B-lineage and T-lineage ALL, without further categorization [50–53].

Classification of acute leukemias (B- or T-lineage ALL and AML) is based on reactivity patterns obtained with a panel of lineage-associated antibodies [54–56]. Immunophenotyping is also essential for distinguishing between ALL and AML; errors in differentiating between these two types of acute leukemias can occur in up to 10% of cases [57–60]. Essential monoclonal antibodies for detecting acute leukemia are presented in Table 40.6.

The B-lineage phenotype ALL, positive for the following: B cell markers CD19, CD20, CD22, TdT, cytoplasmic CD79a, CD34 and CD10. It has been sub-classified according to maturation stage into: early pre B (pro-B), pre-B, transitional (or late) pre-B and (mature) B-ALL [41, 61]. Indifferent regions, various incidences of B-lineage ALL have been reported. Burkitt’s leukemia displays an immunophenotype consisting of mature B cells [55].

T-lineage ALL can also be categorized into phenotypic subgroups, correlating to differentiation stages of thymic T cells. T cell markers are cytoplasmic CD3 and CD7 plus CD2 or CD5. This lineage can be further subdivided into early, mild or late thymocyte differentiation [40, 62].

The Immunophenotyping and genotyping as standard diagnostic techniques have replaced FAB morphological classification; the latter is no longer used as a prognostic factor for acute leukemias [42, 58]. Prior to 2008, the WHO Classification listed B lymphoblastic leukemia as “precursor-B lymphoblastic leukemia.” This terminology is still frequently used in the published literatures, of childhood ALL, to distinguish it from mature B-ALL [63], which is associated with FAB L3 morphology, and which needs a totally different treatment strategy. Mature B-ALL is relatively rare.

**Table 40.6** Monoclonal antibody panel for acute leukemia

Acute leukemias of ambiguous lineage
<b>Acute undifferentiated leukemia</b> <b>Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1</b> <b>Mixed phenotype acute leukemia with t(v;11q23); MLL rearranged</b> <b>Mixed phenotype acute leukemia, B-myeloid, NOS</b> <b>Mixed phenotype acute leukemia, T-myeloid, NOS</b> Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma
B lymphoblastic leukemia/lymphoma
<b>B lymphoblastic leukemia/lymphoma, NOS</b> <b>B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities</b> <b>B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2);BCR-ABL 1</b> <b>B lymphoblastic leukemia/lymphoma with t(v;11q23);MLL rearranged</b> <b>B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) TEL-AML1(ETV6-RUNX1)</b> <b>B lymphoblastic leukemia/lymphoma with hyperdiploidy</b> <b>B lymphoblastic leukemia/lymphoma with hypodiploidy</b> <b>B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) IL3-IGH</b> <b>B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1</b>
T lymphoblastic leukemia/lymphoma

### 40.4.7 Cytogenetic

The WHO classification of “B lymphoblastic leukemia” or “T lymphoblastic leukemia” is based on the findings of specific karyotype and cytogenetic abnormalities, including hyperdiploidy, hypodiploidy, (t[9;22]), t(12;21), t(5;14), and t(1;19) and MLL rearrangement, [34].

Hyperdiploidy (>50 chromosomes) and trisomy 4 and 10 have an excellent prognosis with antimetabolite-based therapy.

t(12;21)(p13;q22) and ETV6-RUNX1 (formerly known as TEL-AML1) positive ALLs carry an excellent prognosis with intensive Asparaginase therapy. t(9;22)(q34;q11.2) and positive ALL BCR-ABL1 positive ALL treated with Imatinib plus intensive chemotherapy have been reported to improve treatment outcome [34].

### 40.4.8 CNS Diagnostic

Cell count, protein, glucose and culture.

Diagnosis of CNS leukemia: Presence of more than 5 WBCs/mm<sup>3</sup> in the CSF

CNS involvement in leukemia is classified as follows:

- CNS 1 < 5 WBCs/mm<sup>3</sup>, no blasts on cytocentrifuge slide
- CNS 2 < 5 WBCs/mm<sup>3</sup>, blasts on cytocentrifuge slide
- CNS 3 > 5 WBCs/mm<sup>3</sup>, blasts on cytocentrifuge slide [64]

If a lumbar puncture is traumatic in a patient with peripheral blasts, CNS disease is diagnosed if:

- CSF WBC is greater Blood WBC
- CSF RBC Blood RBC

**Imaging** Chest x-ray: Mediastinal mass in T cell leukemia. Bone radiography (if indicated)

## 40.5 Treatment Approaches

Acute lymphoblastic leukemia is a systemic disease, and chemotherapy is the main treatment for this disease. The principal treatment of ALL is risk-adapted therapy. It depends on the individual biological factors of ALL (clinical manifestation, laboratory findings on morphology, cytochemistry, Immunophenotyping, and molecular cytogenetic), and initial response to therapy is now used in concert to personalize treatment for all patients. The treatment of ALL is subdivided into remission induction, consolidation with CNS prophylaxis and maintenance phase. Beside refinements in drug treatment, to improved control of the primary disease supportive care played a role in the treatment of ALL [65, 66]. Supportive care is an important issue, including: Infection control, compliance, psychology mentoring, availability of isolation room, intensive care unit, blood bank, antibiotic and anti fungal [67–70].

### 40.5.1 Remission Induction

The aim of remission-induction phase is to eradicate more than 99% of the initial leukemic cell burden and to restore normal hemopoiesis [71].

A three-drug induction regimen seems sufficient for most standard-risk cases.

Combination steroid, vincristine and L-Asparaginase will achieve 95% remission.

Remission achieved if <5% blasts found in bone marrow at the end of induction period. Decrease of hemoglobin, white blood cells and platelet also occurred in parallel of induction treatment. Duration of this period is 4–5 weeks. Intrathecal methotrexate is given in this period to prevent CNS involvement [66, 72].

### 40.5.2 Consolidation

This continuation treatment aimed to prevent reappear leukemic cells and to reach a complete eradication of leukemic cells. Without treatment in this period, leukemic cells will appear within weeks or months [73].

### **40.5.3 Maintenance**

This period aimed to prevent recurrence of leukemic cells. Duration of this period is 1.5–2 years, using combination of daily 6-MP and once weekly MTX [74, 75].

### **40.5.4 Complication and Side Effects**

- Tumor lysis syndrome (TLS): Prophylactic treatment TLS in hyperleukocytosis patients. Life-threatening metabolic complications can result from tumor lysis syndrome (spontaneous leukemic cells turnover and chemotherapeutically induced leukemic cell death), presenting with hyperuricemia, hyperkalemia and hyperphosphatemia [76, 77]
- Anemia: Transfusion is needed if hemoglobin level below 6 g/dl [78]
- Bleeding: due to thrombocytopenia as an impact of suppressing leukemic cells and or cytotoxic drugs. It needs platelet transfusion if bleeding occurred and platelet level < 30.000/dl [79, 80]
- Infection: Bacterial, fungal or viral may be occurred, usually the symptom is atypical especially during neutropenia phase.
- High-risk infection during induction phase and during the condition of absolute neutrophil counts <500/dl. Isolation room is needed to care this condition, and immediate starts to give broad-spectrum antibiotics. Sometimes combination with anti fungal and or anaerobe antibiotics are needed. When pneumocystis carinii pneumonia occurred (usually after induction treatment): high-dose trimethoprim-sulfamethoxazole: 20 mg trimethoprim/kg body weight [81, 82]

## **40.6 Prognostic Factors**

Studies in the United States and Europe have shown the importance of clinical and biologic characteristics as prognostic factors in childhood ALL [64, 71]. (Table 40.7.)

## **40.7 Future Developments**

The success of leukemia treatment is increasing. Accurate diagnosis supports the success in management of ALL. An individual based treatment is now started to apply in some developed countries, but in most developing countries where the majority of pediatric malignancies are found and resources are limited, the management of ALL is a big problem. A local adapted treatment should be implemented in this circumstances.

**Table 40.7** Prognostic factors in childhood ALL

Factors	Favorable	Unfavorable
Age	>1 year to <10 years	<1 year or >10 years
WBC	<50,000/mm <sup>3</sup>	>50,000/mm <sup>3</sup>
Immunophenotyping	B-lineage	T-Lineage
Chromosome count	>50	<45
DNA index	> 1.16	< 1.16
MRD (end of induction)	<0.01%	>1%
Response to steroid on D7	≤1000/mm <sup>3</sup>	>1000/mm <sup>3</sup>

**Key Points**

- Acute leukemia is a curable disease and the most common malignancy in children
- Incidence of this disease increasing
- Diagnosis is made based on immunologic and genetic/molecular examination
- The recent treatment modalities increasing survival rate.

**Multiple-Choice Questions**

1. A 6-year old boy presents to you with general lymphadenopathy in the neck, axillar and groins. He has high fever for 4 days and looks pale with gum bleeding, petechiae and hepato-splenomegaly. The chest X-ray detects a mediastinal mass. The diagnosis is most likely:
  - (a) Tuberculosis
  - (b) Burkitts Lymphoma
  - (c) Hodgkins Lymphoma
  - (d) Non-Hodgkins Lymphoma
  - (e) **T-cell Leukemia**
2. The childhood acute leukemia which characteristics are related to hyperleukocytosis, testicular, and mediastinal mass belongs to:
  - (a) B-ALL
  - (b) **T-ALL**
  - (c) AML-M2
  - (d) AML-M1
  - (e) CML
3. Early response to treatment may be assessed using the light microscopy at day 7 of induction treatment. Patients are classified as good responders when:
  - (a) Peripheral blasts count 5000–10,000/microliter
  - (b) **Peripheral blasts count less than 1000/microliter**
  - (c) No cytopenias in complete blood count
  - (d) Blasts on the marrow 6–25%
  - (e) Blasts on the marrow less than 5%

4. Treatment of childhood ALL is based on the risk stratification system. The National Cancer Institute (NCI)/Rome working group classifies patients into standard and high risk groups. The following patients fulfills the standard risk group:
  - (a) A boy, 13 years old, white blood cell count 5000/microliter, without mediastinal mass
  - (b) A boy, 9 years old, white blood cell count 51,000/microliter, B-cell ALL
  - (c) A girl, 7 years old, white blood cell count 15,000/microliter, T-cell ALL
  - (d) **A girl, 7 years old, white blood cell count 15,000/microliter, B-cell ALL**
  - (e) A boy, 7 months old, white blood cell count 15,000/microliter, B-cell ALL
  
5. Induction treatment in childhood ALL traditionally consists of vincristine, asparaginase, intrathecal therapy, steroid, and anthracycline. In terms of steroids, dexamethasone may replace prednisone based on the following considerations:
  - (a) Dexamethasone is much less toxic than prednisone
  - (b) Dexamethasone induces greater appetite than prednisone thus give more benefit against the side effect of chemotherapies that usually lead to nausea and depressed appetite
  - (c) There is no evidence that prednisone showed benefit in ALL treatment
  - (d) **Prednisone shows less ability to penetrate blood brain barrier thus less effective to prevent CNS involvement**
  - (e) Prednisone may induce severe gastritis than dexamethasone
  
6. Acute tumor lysis syndrome is an emergency case and may be life-threatening in childhood ALL. Which of the following statements about it is correct?
  - (a) It commonly occurs during maintenance phase of treatment
  - (b) It consists of triad of hyperuricemia, hyperphosphatemia and hypokalemia
  - (c) It may lead to renal failure, thus needs water restriction
  - (d) It may lead to blood viscosity due to hyperleukocytosis, thus need aspilet as blood thinner
  - (e) **Treatment modalities consist of hyperhydration, allopurinol or urate oxydase and sodium bicarbonate**
  
7. Which of the following findings refer to extremely poor prognosis in infants <1 year old with ALL:
  - (a) Age 6–11 months
  - (b) Central nervous system involvement
  - (c) Initial white blood cell count 50,000–100,000/microliter
  - (d) B-cell ALL
  - (e) **Age less than 3 months and MLL translocations**
  
8. The treatment modality for ALL that may induce the development of secondary AML is:



- (a) Methotrexate
- (b) Anthracyclines
- (c) Steroids
- (d) Vincristine
- (e) **Epipodophyllotoxins**

9. Chemotherapies for ALL that shows cumulative dose-related toxicity is:

- (a) Etoposide
- (b) Methotrexate
- (c) **Anthracyclines**
- (d) L-asparaginase
- (e) 6-Mercapto purine

10. The prognostic factors at the 1st relapse that influence the outcomes after relapse in childhood ALL is:

- (a) The intensity of treatment prior to relapse, the more intensive it is the better outcome
- (b) Age at diagnosis, more than 10 years has better outcome than age less than 1 year
- (c) **Duration of 1st remission to relapse, less than 18 months has worse outcomes than 36 months or more**
- (d) Immunophenotype, T-ALL shows better outcome than B-cell ALL
- (e) Sex, boys have better outcomes than girls

### Clinical Case

1. In a country in south east Asia, a 7-year old boy was referred from primary health care to the tertiary Hospital with complaints of gum bleeding, fever, malaise. On physical examination found pale, body temperature was 38.8 C, hepatomegaly and splenomegaly (Schuffner-3). A routine lab result reveals Hgb 8.0 g/dL, platelet count 29,000/microliter, and white blood cell count of 81,000/microliter. Pathologist found difficulties in making FAB classification of bone marrow aspirate. They conclude of mixed leukemia (found myeloblast and lymphoblast). Immunophenotyping result: CD34 (+) CD7 (+) dim, CD19(+), cyCD79a (+) and CD10(+). Cytogenetic studies not available. Conclusion: B-ALL Lesson to learn: In developing countries, where health facilities are limited, a case like this often occurred. The importance of Immunophenotyping examination to conclude the hematology malignancies is urgently needed.
2. A 5-year old boy came to clinic with complaints of gum bleeding, fever, malaise and on physical examination found hepatosplenomegaly. A routine lab result reveals Hgb 7.0 g/dL, platelet count 21,000/microliter, and white blood cell count of 71,000/microliter with 86% eosinophils. A bone marrow aspirate showed 7% lymphoblasts and markedly increased eosinophil precursors. Cytogenetic studies of the bone marrow show 46,XY,t(5;14)(q31;q32) [18]/46,XY [2]. The diagnosis is: acute lymphoblastic leukemia. Discussion: The presence of a chromosome translocation in most or all cells is generally

showed a malignancy. In this case, ALL can be associated with marked eosinophilia in cases with a t(5;14) that brings the IL-3 gene from chromosome 5q31 into the vicinity of the immunoglobulin heavy chain locus. In some patients have very low percentages of marrow blasts. The eosinophils are reactive and not part of the malignant clone.

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# Chapter 41

## Myelodysplastic Syndromes



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**Abstract** Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell (HSC) malignancies that represent a heterogeneous group characterized by ineffective hematopoiesis, dysplasia in one or more myeloid cell lineages and an increased risk of developing acute myeloid leukemia. Most of MDS patients are elderly and anemia is the most prevalent cytopenia. MDS are classified based on percent of bone marrow and peripheral blood blasts, type/number of dysplastic cell lineages, presence of ring sideroblasts and chromosomal abnormalities, which are present in up to 50% of cases. The pathogenesis of MDS is complex and involves RNA splicing, DNA modification, chromatin regulation and cell signaling. The prognosis depends mainly on the marrow blast percentage, number and extent of cytopenias and cytogenetic abnormalities. Patients with multiple cytopenias and complex karyotype present overall survival of less than 1 year. In the other hand, cases with normal cytogenetics, isolated anemia, and no increase in number of blasts may present overall survival of 5 or more years. The goals of the therapy, in lower risk patients, are to improve the cytopenias, while to higher risk cases are to delay the progression to acute leukemia and to improve overall survival.

**Keywords** Myelodysplastic syndromes · Cytopenias · Cytogenetics

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## Abbreviations

MDS	Myelodysplastic Syndromes
AML	acute myeloid leukemia
BM	bone marrow
BMT	Bone marrow transplantation
CBC	complete blood count
EPO	recombinant erythropoietin
ESA	erythropoietin stimulating agents
FAB	French – American – British
HSC	hematopoietic stem cell
IPSS	International Prognostic Scoring System
RBC	Red blood cells
WHO	World Health Organization

### 41.1 Introduction

Myelodysplastic Syndromes (MDS) refers to a large spectrum of clonal hematopoietic stem cell (HSC) disorders characterized by the presence of cytopenia(s), normo/hypercellular bone marrow (BM) with dysplasia and ineffective hematopoiesis [1–3]. This paradox (cytopenia with normo/hypercellular BM) is the result of, at least in early forms of the disease, apoptosis of hematopoietic cells [4].

The cytopenia can be limited to a single cell line, resulting in isolated anemia, thrombocytopenia, or neutropenia, or may be presented in two or all bone marrow lineages with bicytopenia or pancytopenia respectively [5]. Because most patients present with anemia which was resistant to iron and other common treatments, MDS was formerly commonly referred to as refractory anemia [1]. The damaged stem cell in MDS loses the normal ability to differentiate into end-stage cells due to abnormal clone which suppresses normal hematopoiesis and becomes increasingly dysplastic, ultimately resulting in fatal pancytopenia or progression to acute myeloid leukemia (AML) which occurs in up to 30% of the cases [5–8].

The diagnosis of MDS is based on persistent cytopenia, bone marrow dysplasia (in one or more hematopoietic cell lineage(s) and cytogenetic abnormalities. Of utmost importance, the cytopenias and bone marrow dysplasia must not be related to renal disease, iron deficiency, folate/b12 deficiency, infectious disorders (hiv, hcV), Hypothyroidism and others. The most common chromosomal abnormalities are related to chromosome del(5q), -7,del(7q) and +8 [9–13].

MDS is a heterogeneous disorder and the clinical course is highly variable, ranging from stable disease over 10 or more years to death within a few months due to leukemic transformation. The evaluation of disease risk and outcome of patients with MDS is one of the most critical points due to this impressive clinical heterogeneity [2, 3, 14, 15].

## 41.2 Epidemiology

Idiopathic MDS is rare occurring at a frequency of approximately 1 per 100,000 per year in general population. However, the incidence increases dramatically with age, with an incidence of 25–50 per 100,000 per year in population older than 60 years old, which makes MDS the most common bone marrow cancer in occidental world [16, 17]. Thus, approximately, 75% of MDS patients are older than 60 years of age at diagnosis and the incidence rate doubles each decade over 40 years of age [2, 3, 14, 15].

The incidence and clinical characteristics of patients with MDS varies by geographical area, and this has been attributed to genetic or ethnic, occupational, lifestyle, and environmental factors, that have not been fully elucidated [18, 19].

Ethnic differences and regional influences may play a role in the pathogenesis of MDS [18]. In the United States, Surveillance Epidemiology and End Results (SEER) data suggest that the incidence rates of MDS were highest among whites and non-Hispanics than in blacks [20]. Japanese patients with refractory anemia (RA), according to the French – American – British (FAB) – classification [1] are usually younger with more severe cytopenia, lower percentage of abnormal karyotypes and a more favorable prognosis than German patients [18, 21], and has higher frequencies of MDS-unclassified (MDS-U) with pancytopenia and refractory cytopenia with unilineage dysplasia (RCUD), according to the World Health Organization (WHO) 2008 classification [22]. Another comparative study from New Zealand and Australia described epidemiological characteristic based on cancer registration and found a higher median age at diagnosis and higher male/female (M/F) ratio, which increases with age [23]. The leading cohort from Italy showed a lower age at diagnosis, a higher frequency of RA/RCUD/5q and of low risk-IPSS patients than the validation cohort from Germany [24].

We reported the largest series of Latin American MDS patients (Brasil, Argentina and Chile) which was composed of 1080 cases. This was the first study from South-America, which attempted to describe demographic, clinical features, and outcome of MDS patients. We retrospectively analyzed 1080 patients with de novo MDS from Argentina (635), Brazil (345), and Chile (100). Chilean patients were younger, with female preponderance. Brazilian series showed a higher predominance of RARS subtype regarding FAB and WHO classifications. Hemoglobin levels were significantly lower in Brazilian and Chilean series and Chilean series also showed a lower platelet count with no differences concerning the neutrophil count, % BM blast, and the distribution of cytogenetic risk groups. Chilean series depicted a lower overall survival (OS; 35 months vs. 56 months-Argentina; 55 months Brazil), which was consistent with a higher predominance of the high-risk group according both to the IPSS and IPSS-R. The IPSS-R system and its variables showed a good reproducibility to predict clinical outcome for the whole South-American population. Epidemiological and clinical characteristics, distribution among prognostic subgroups, the Overall survival, and the access to disease modifying therapies were more similar between Argentinean and Brazilian compared with Chilean MDS series [25].



### 41.3 Risk Factors

The risk factors for developing MDS are:

1. Age: population studies in the United Kingdom have found that the crude incidence increases from 0.5 per 100,000 people under the age of 50 years to 89 per 100,000 people 80 years of age or older. The mechanism responsible for the association between aging and MDS is not known, but it can be postulated that inherent age-associated impairment of DNA repair may increase the likelihood of mutations, which, in turn, lead to the emergence of these clonal proliferative disorders. We have demonstrated the influence of functional polymorphisms in DNA repair genes of myelodysplastic syndrome as well as expression of DNA repair genes are related to MDS subtypes and age [26, 27].
2. Genetic predisposition: familial syndromes have been reported, but are rare. Inherited predisposition to the disorder is evident in a third of pediatric cases, including children with Down's syndrome, Fanconi's anemia, and neurofibromatosis [28].
3. Environmental exposures, particularly to benzene and its derivatives, as well as exposures to radiation (e.g. the medical effects of Nagasaki Atomic Bombing). The Nagasaki University School of Medicine reported that radiation was released in addition to the ferocious blast wind and heat rays. It is believed that 50%, 35% and 15% of the total energy output was blast, heat and radiation. Patients with hypocellular pattern in bone marrow were reported with dysplastic changes. Of utmost importance, the radiation induced chromosomal aberrations in hematopoietic stem cells among atomic bomb survivors exposed to a radiation dose of 100 cGy (1 centigray = 1 rad) or more radiating [13, 29, 30].
4. Prior therapy, including radiation treatment, alkylating agents (i.e. chlorambucil, cyclophosphamide, melphalan, nitrosourea and procarbazine), and purine analogues [13, 31, 32] For alkylating agents, the risk of developing a secondary MDS or AML starts with the end of therapy and peaks at 4 years, with a plateau at 10 years [33]. Of utmost importance, these cases show deletion of chromosome 7 or monosomy 7 with grim prognosis.
5. Pesticides. Jin et al., demonstrated, in a meta-analysis including 1942 cases and 5359 controls (11 case-control studies), a correlation between pesticide exposure and a statistically significant increased risk of MDS (OR = 1.95, 95% CI 1.23–3.09) [33].
6. Hair Dye [34].
7. Alcohol and Cigarette Smoke. The habit of smoking cigarettes and consuming alcoholic beverages are also related to MDS and are commonly described in the scientific literature [35, 36].

## 41.4 Pathology, Cytogenetic and Molecular Mechanisms

Up to 30% of MDS patients are at risk to transform to acute leukemia. The identification of chromosomal abnormalities is crucial to determine survival and predict the risk of a transformation to acute leukemia. The most common chromosomal abnormalities are del(5q), -7, del(7q), +8, del(20q) and -Y. A large proportion of MDS patients (40–65%) present normal karyotypes at diagnosis. In this group, which is highly heterogeneous from a biological standpoint, outcome is often unpredictable. The pathophysiology of MDS and its progression to AML involve cytogenetic, genetic, and epigenetic aberrations [28]. It is multifactorial and depends on the interaction between aberrant hematopoietic cells and their microenvironment.

Over the past years, major signal transduction molecules have been identified and their genetic alterations have been extensively analyzed in MDS. These include receptors for growth factors, RAS signaling molecules, cell cycle regulators and transcription factors [10]. Regarding the cell cycle regulators, we demonstrated that Proteins of the mitotic checkpoint and spindle are related to chromosomal instability and unfavorable prognosis in patients with myelodysplastic syndrome. We detected that Higher Aurora-B expression was found in patients with an abnormal versus normal karyotype while High expression of MAD2 and CDC20 was associated with severe thrombocytopenia. We also found statistically significant differences in the overall survival rate when comparing different degrees of CDC20, MAD2 and Aurora-B protein expression [37]. Many specific pathways of chronic inflammation are involved in MDS pathophysiology and have been described recently. These include abnormal activation of innate immune signals, elevated levels of proinflammatory cytokines and aberrations in their signaling pathways, suggesting that an inflammatory process may act as a pathogenic driver [38–40].

Recently, we demonstrated that significantly elevated levels of IL-8 and NF- $\kappa$ B were increased in MDS patients, with positive association of NF- $\kappa$ B with some markers of poor prognosis. A positive correlation between IL-8 and NF- $\kappa$ B suggests they cooperate as part of a complex networking of immune and inflammatory factors involved in MDS [38].

MDS pathogenesis involves multiple steps through a sequence of genetic lesions in the DNA of HSC [41], which lead to functional changes in the cell and the emergence and subsequent evolution of AML [42]. DNA damage can result from many reasons, such as environmental genotoxic exposure [43], internal genotoxic stress (i.e. reactive oxygen species [44], UV irradiation [45] and chemical changes that can occur in a single strand or both strands of DNA [46]. We have reported that many polymorphisms of genes related to DNA Damage and its expression are truly associated to MDS pathogenesis. Patients with hypocellular MDS show significantly decreased expression of *ATM*, *BRCA1*, *BRCA2*, *LIG4* and *ERCC8* than those with normocellu-

lar/hypercellular bone marrow, whereas *XPA* and *XPC* are increased. In patients with hypoplastic MDS, a low expression of *ATM*, *LIG4* ( $p = 0.0199$ ) and *ERCC8* is significantly associated with the presence of chromosomal abnormalities [47].

Very recently, we detected the association between Xeroderma Pigmentosum DNA repair genes (*XPA* rs1800975, *XPC* rs2228000, *XPD* rs1799793 and *XPF* rs1800067) polymorphisms and myelodysplastic syndrome (MDS). To assess the functional role between these polymorphisms and MDS, we evaluated 189 samples stratified in two groups: 95 bone marrow samples from MDS patients and 94 from healthy elderly volunteers used as controls. Genotypes for all polymorphisms were identified in DNA samples in an allelic discrimination experiment by real-time polymerase chain reaction (qPCR). We also studied the mRNA expression of *XPA* and *XPC* genes to evaluate if its polymorphisms were functional in 53 RNA MDS patients by qPCR methodologies. To the rs2228000 polymorphism, the CT and TT polymorphic genotype were associated with increased odds ratio (OR) of more profound cytopenia (hemoglobin and neutrophils count). To the rs1799793 polymorphism, we found that the GG homozygous wild-type genotype was associated with a decreased chance of developing MDS. We observed low expression of *XPA* in younger patients, in hypoplastic MDS and patients with abnormal karyotype when presented AG or AA polymorphic genotypes. All these results reinforces that DNA repair genes are part of MDS pathogenesis [48].

Considering the clinical heterogeneity of MDS, Bejar et al., in 2012 [49] used a combination of next-generation sequencing and mass spectrometry-based genotyping to identify mutations in 439 samples of bone marrow aspirate from MDS patients. This was the first and the most significant work to demonstrate the importance of mutations in the prognostic of MDS [49]. A total of 51% of all patients had at least one point mutation, including 52% of the patients with normal cytogenetics. Bejar et al. [47], detected that Mutations in *RUNX1*, *TP53*, and *NRAS* were associated with severe thrombocytopenia and an increased proportion of bone marrow blasts, all markers of grim prognosis. In a multivariable Cox regression model, the presence of mutations in five genes retained independent prognostic significance: *TP53*, *EZH2*, *ETV6*, *RUNX1* and *ASXL1* [50].

In 2013, Papaemmanuil E [51] reinforced the importance of Mutations in MDS, sequencing 111 genes from 738 patients with MDS to explore the role of acquired mutations in MDS. This work demonstrated that 78% of patients had 1 or more oncogenic mutations. The authors identified very complex patterns of pairwise association between genes, indicative of epistatic interactions involving components of the spliceosome machinery and epigenetic modifiers. This work clearly demonstrated that most genes mutated in MDS were related to RNA splicing, DNA modification, chromatin regulation, and cell signaling [51].

## 41.5 Diagnosis

The diagnosis of MDS is based on clinical features, complete blood count (CBC), bone marrow analysis, cytogenetic data and molecular profile [52]. Despite this, it is important to remember that MDS is a diagnosis of exclusion. Thus, an extensive diagnostic investigation is necessary to establish MDS. Consequently, all other causes of cytopenia must be carefully excluded.

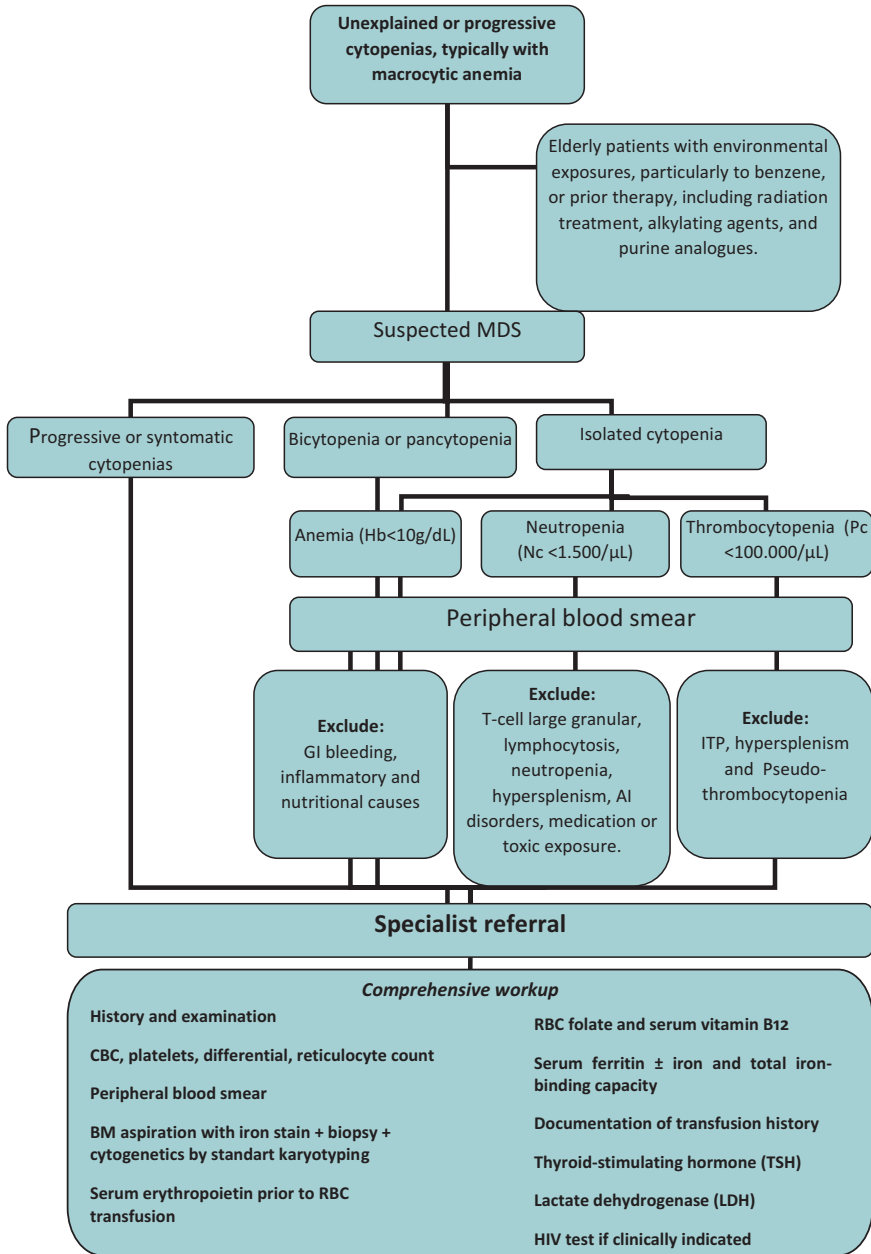
The list includes vitamin deficiencies (especially vitamin B12 and folate), autoimmune disease, liver disease, hemolytic anemia, hypersplenism, effects of a drug, infections, exposure to environmental toxins, aplastic anemia, paroxysmal nocturnal hemoglobinuria, BM infiltration by malignancy and rare forms of hereditary anemias (such as congenital dyserythropoetic anemias) [6, 28]. A flowchart about the diagnosis workup and referral of patients with MDS is presented in Fig. 41.1.

### 41.5.1 Clinical Features

The clinical manifestation of MDS is nonspecific and highly variable, depending on the MDS subtype, and it ranges from indolent to life threatening [53]. Many patients are asymptomatic. Nevertheless, the majority of cases present anemia (in up to 80% of patients) with symptoms of fatigue, shortness of breath, palpitations, thrombocytopenia (bruising, petechiae or bleeding) or neutropenia (fever, recurrent or prolonged infections) [12, 54]. In up to 14% of the cases, auto-immunity may be present principally related to del(5q) or IRF-1 expression [55, 56].

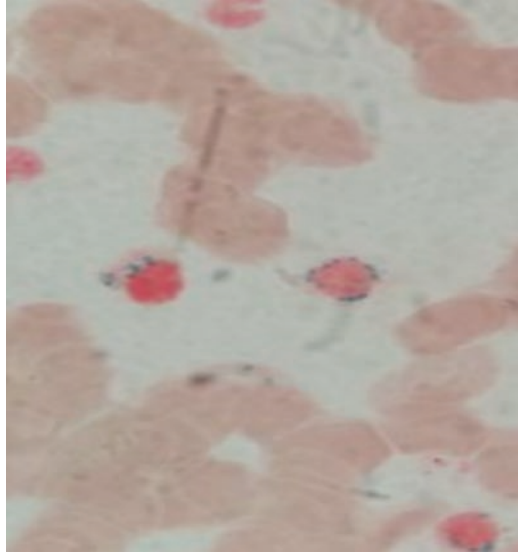
### 41.5.2 Peripheral Blood

Cytopenia is a “sine qua non” for any MDS diagnosis. The diagnosis of MDS is generally suspected based on the presence of an abnormal CBC [3]. Anemia, typically macrocytic and non-regenerative, is the most common peripheral blood abnormality and occurring in approximately 80% to 85% of patients. Thrombocytopenia occurs in 30%–45% of MDS cases and 40% of patients have neutropenia at diagnosis. Neutropenia and thrombocytopenia are rarely detected without anemia [28, 57] and is reported in less than 5% of adults [7]. Blasts can be found in peripheral blood, but rarely exceeding 5% [28].



**Fig. 41.1** Flowchart: Diagnosis workup and referral of patients with myelodysplastic syndromes (MDS). *AI* autoimmune, *BM* bone marrow, *CBC* complete blood count, *GI* gastrointestinal, *ITP* idiopathic thrombocytopenic purpura, *NCCN* National Comprehensive Cancer Network, *RBC* red blood cell. Modified from Foran et al. 2012 and NCNN guideline version 1.2018 – Myelodysplastic syndromes

**Fig. 41.2** Ring sideroblasts from a patient with myelodysplastic syndrome. This picture shows the iron-loaded mitochondria, visualized by Prussian blue staining (Perls' reaction), encircling at least one-third of the erythroid nuclear circumference with as a perinuclear ring of blue granules

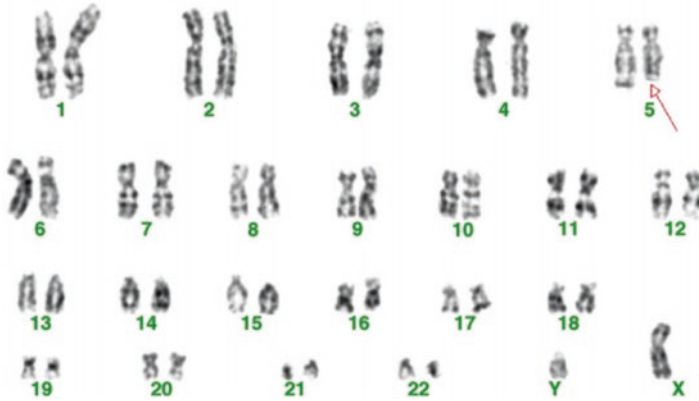


### ***41.5.3 Bone Marrow Analysis (Core Biopsy and Bone Marrow Smear)***

The marrow is best examined using needle biopsy and smeared preparation. Both procedures provide different information. The BM aspirate allows for detailed evaluation of cellular morphology and evaluation of percent of blasts. The BM biopsy allows for determination of bone marrow cellularity and architecture [3, 58]. The cellularity is best evaluated in biopsy specimens, because the apparent cellularity of aspirates may be misleading. Usually, the marrow cellularity is normal or hypercellular in up to 80% of MDS patients [26].

The morphologic features of MDS include ring sideroblasts (where five or more iron granules encircle at least one-third of the nuclear circumference) [7] (Fig. 41.2) neutrophils with only two nuclear lobes (the pseudo-Pelger-Huët anomaly) or abnormal cytoplasmic granulation, and multinucleated or small megakaryocytes with simple nuclei [13]. The dyserythropoiesis is also characterized by nuclear or cytoplasmic asynchrony, cytoplasmic vacuolization, bizarre multinucleation, irregular nuclear lobulations, and increased karyorrhexis [7].

The bone marrow study is also useful to application of immunohistochemistry; Fluorescent in Situ Hybridization (FISH) and flow cytometry.



**Fig. 41.3** Bone marrow karyotype from a patient with a 5q- syndrome showing the deletion. 46, XY, del(5q)(q15q33)[4]/46, XY[16]

#### 41.5.4 Cytogenetic Tests

Conventional karyotyping remains an essential component of the diagnostic work-up of any patient with suspected MDS [6, 28, 59]. Cytogenetics is of importance to determine prognosis of patients and may also drive treatment [3, 7, 28]. Chromosomal anomalies are detected in approximately 50% of patients with primary MDS [6, 11] and in up to 80% of patients with MDS secondary to chemotherapy or other toxic agents (with increased blasts) [11].

The cytogenetic features include partial or complete loss or gain of chromosomes. The most frequent findings being del(5q), -7 or del(7q), +8, deleted 20q, and deleted 17p, but complex cytogenetic findings are common in patients with a major excess of marrow blasts or with therapy-related MDS (Fig. 41.3) [28].

#### 41.5.5 Molecular Tests

Targeted sequencing of a limited number of genes can detect mutations in up to 90% of MDS cases. The most reported are *SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, *RUNX1*, *U2AF1*, *EZH2* AND *TP53*.

Considering the WHO Classification of Hematological Malignancies updated in 2016, only two are routinely recommended: (1) Evaluation of *TP53* in cases with del(5q) because it is associated with grim prognosis; (2) In a case of MDS if ring sideroblasts (RS) comprise as few as 5% of nucleated erythroid cells, because the presence of *SF3B1* mutation establishes the diagnosis of MDS with RS.

### 41.5.6 Other Tests

#### – Immunohistochemistry

This assay includes the detection of anomalous expression of CD34, CD117/c-kit and lineage markers in immature blood cells [58].

- FISH- Several studies have compared FISH and conventional cytogenetic analysis at specific times during the development of MDS, most of them showing only a small advantage of FISH for detecting chromosomal anomalies. We performed I-FISH and conventional karyotyping (G-banding) on 50 MDS patients at diagnosis, after 6 and 12 months or at any time if a transformation to acute myeloid leukemia (AML) was detected. Applying a probe-panel targeting the centromere of chromosomes 7 and 8, 5q31, 5p15.2 and 7q31, we observed one case with 5q deletion not identified by G-banding. I-FISH at 6 and 12 months confirmed the karyotype results. FISH for MDS should be performed when cytogenetic analysis presents without metaphases or less than 20 cells were analyzed [59, 60].
- Flow cytometry – Several groups have published flow cytometry scores and guidelines useful for the diagnosis and/or prognosis of MDS, which are mostly based on detecting immunophenotypic abnormalities in granulocyte, monocyte, and lymphoid lineages. All these evaluations add to other tests when confirming that dysplasia is due to bone marrow disorder [59, 60].

## 41.6 Prognosis and WHO Classification

In 1997, the International Prognostic Scoring System (IPSS) [14] was adopted as the first universal prognostic system for MDS. The IPSS applied multivariate analyses to identify factors with independent predictive power for the risk of AML transformation and overall survival, such as the BM blast percentage, the number of cytopenias, and the cytogenetic subgroup (good, intermediate, and poor prognosis). Thus, as an individual's score increases (e.g. with a higher blast percentage, less favorable cytogenetics, and multiple cytopenias), the chance of transforming to AML increases, and survival expectation declines.

In 2012, Greenberg et al. [15], refined the IPSS by reassessing the prior major predictive features, determining the impact of the newer clinical features for prognostic power and incorporating more differentiated cytogenetic subgroups. Of utmost importance, they detected, in Multivariate analyses, that the same major features present in the IPSS (cytogenetic subgroups, marrow blast percentage, and cytopenias) retained major prognostic impact in IPSS-R, but more precise prognostication of survival and AML evolution in the IPSS-R was demonstrated by effective refinement of these features within the IPSS-R (depth of cytopenias, splitting of marrow blasts <5%, and more precise cytogenetic subgroups (Tables 41.1 and 41.2) [15].



**Table 41.1** Frequent mutations in MDS-associated genes likely to indicate clonal hematopoiesis and its clinical significance

Mutated gene <sup>1</sup>	Overall incidence	Clinical significance
TET2	20%–25%	Associated with normal karyotypes.
DNMT3A	12%–18%	Associated with a poor prognosis in patients without SF3B1 mutations.
ASXL1	15%–25%	Independently associated with a poor prognosis in MDS
EZH2	5%–10%	Independently associated with a poor prognosis in MDS
SF3B1	20%–30%	Strongly associated with ring sideroblasts. Independently associated with favorable prognosis.
SRSF2	10%–15%	More frequent in CMML(40%) and associated with a poor prognosis
U2AF1	8%–12%	Associated with a poor prognosis
ZRSR2	5%–10%	Associated with a poor prognosis
TP53	8%–12%	Independently associated with a poor prognosis. More frequent with complex karyotypes and del (5q). Most commonly associated with no response to lenalidomide.
NRAS	5%–10%	Associated with a poor prognosis
CBL	<5%	More frequent in CMML (10%–20%) JMML (15%)
JAK2	<5%	More frequent in MDS/MPN-RS-T (50%)
NF1	<5%	More frequent in CMML (5%–10%) and JMML (30%) where is often germline.
RUNX1	10%–15%	Independently associated with a poor prognosis in MDS. May be familial and associated with low platelets count
ETV6	<5%	Independently associated with a poor prognosis. May be familial in very rare cases.
IDH1	<5%	More frequent in AML
IDH2	<5%	More frequent in AML and associated with a poor prognosis.

Adapted from Bejar [41] and Papaemmanuil [51]

The comorbidities are very important to determine overall survival of MDS, a disorder of elderly. Frailty, disability and physical functioning were evaluated to predictive overall survival (OS) in 445 consecutive patients with MDS and chronic monomyelocytic leukaemia. OS was significantly shorter for patients with higher frailty and comorbidity scores, any disability, impaired grip strength and timed chair stand tests. By multivariate analysis, the age-adjusted IPSS-R, frailty and Charlson comorbidity score were independently prognostic of OS. All these parameters must be evaluated before deciding any treatment or using the revised IPSS [61].

MDS have been classified according to the FAB proposals since 1982 [1]. Thereafter proposals of WHO added morphologic refinement of the FAB classification [62]. The latest proposal of the WHO classification is compiled in Table 41.3.

**Table 41.2** Revised International Prognosis Scoring System (IPSS-R)

Prognostic Variable	Risk Score						
	0	0,5	1,0	1,5	2	3	4
<b>Cytogenetics</b>	Very good	–	Good	–	Intermediate	Poor	Very poor
<b>BM blasts</b>	< or = 2%	–	> 2 – < 5 %	–	5–10%	> 10%	–
<b>Haemoglobin (g/dL)</b>	> or = 10	–	8–< 10	<8	–	–	–
<b>Platelets (10<sup>9</sup>/L)</b>	> or = 100	50 - <100	< 50	–	–	–	–
<b>ANC (10<sup>9</sup>/L)<sup>a</sup></b>	> or = 0,8	<0,8	–	–	–	–	–

Modified from Greenberg et al. [15]

Risk category: Very low: ≤1.5; Low: >1.5–3; Intermediate: >3–4.5; High: >4.5–6; Very high: >6  
 Cytogenetic: Very good: -Y, del(11q); Good: Normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones; Poor: -7, inv(3)/t(3q), double including -7/del(7q), complex: 3 abnormalities; Very poor: Complex: >3 abnormalities

–: Indicates not applicable

<sup>a</sup>ANC Absolute neutrophil count

### 41.6.1 Therapy

#### 41.6.1.1 General

It is customary, since the classical IPSS [14], to divide the patients in two groups: Lower risk MDS and Higher Risk MDS. Patients with IPSS low and Intermediate-1 are considered low risk and IPSS High and Intermediate-2 are considered High risk. Patients with RAEB are also considered High risk while cases of Refractory Anemia and RARS are low risk.

The main objective of treating High risk patients is to modify the natural disease course due to increased chance of AML transformation and short survival. Based on this, the treatment includes bone marrow transplantation, whenever possible, hypomethylating agents and chemotherapy (less common) [14].

The main objective of treating Low risk MDS is to treat the symptoms related to cytopenias, mainly fatigue and shortness of breath due to anemia, infections due to neutropenia and bleeding related to thrombocytopenia.

**Table 41.3** WHO classification of myelodysplastic syndrome with laboratory and cytogenetic findings

<i>Types</i>	<b>Peripheral blood (PB) and Bone marrow (BM) findings and cytogenetics of MDS</b>
<i>MDS with single lineage dysplasia (MDS-SLD)</i>	<ul style="list-style-type: none"> <li>• One or two cytopenias<sup>a</sup>.</li> <li>• Ring sideroblasts &lt;15 % of marrow erythroid elements, or &lt;5% if SF3B1 mutation is present.</li> <li>• Bm &lt; 5% of blasts and Pb &lt;1%, no Auer rods.</li> <li>• Any cytogenetics finding, unless fulfills all criteria for MDS with isolated del(5q).</li> </ul>
<i>MDS with multilineage dysplasia (MDS-MLD)</i>	<ul style="list-style-type: none"> <li>• One, two or three cytopenias.</li> <li>• Ring sideroblasts &lt;15 % of marrow erythroid elements, or &lt;5% if SF3B1 mutation is present.</li> <li>• BM &lt; 5% of blasts and Pb &lt;1%, no Auer rods.</li> <li>• Any cytogenetics finding, unless fulfills all criteria for MDS with isolated del(5q)</li> </ul>
<i>MDS with ring sideroblasts (MDS-RS)</i>	
<i>MDS-RS with single lineage dysplasia (MDS-RS-SLD)</i>	<ul style="list-style-type: none"> <li>• One or two cytopenias.</li> <li>• Ring sideroblasts &gt; or = 15 % of marrow erythroid elements, or 5% if SF3B1 mutation is present.</li> <li>• BM &lt; 5% of blasts and Pb &lt;1%, no Auer rods.</li> <li>• Any cytogenetics finding, unless fulfills all criteria for MDS with isolated del(5q)</li> </ul>
<i>MDS-RS with multilineage dysplasia (MDS-RS-MLD)</i>	<ul style="list-style-type: none"> <li>• One, two or three cytopenias.</li> <li>• Ring sideroblasts &gt; or = 15 % of marrow erythroid elements, or &gt; or = 5% if SF3B1 mutation is present.</li> <li>• BM &lt; 5% of blasts and Pb &lt;1%, no Auer rods.</li> <li>• Any cytogenetics finding, unless fulfills all criteria for MDS with isolated del(5q)</li> </ul>
<i>MDS with isolated del(5q)</i>	<ul style="list-style-type: none"> <li>• One, two or three dysplastic lineages.</li> <li>• One or two cytopenias.</li> <li>• None or any ring sideroblasts .</li> </ul>

(continued)

**Table 41.3** (continued)

	<ul style="list-style-type: none"> <li>• BM &lt; 5% of blasts and Pb &lt;1%, no Auer rods.</li> <li>• Del(5q) alone or with one additional abnormality except -7 or del(7q).</li> </ul>
<b><i>MDS with excesso blasts (MDS-EB)</i></b>	
<i>MDS-EB-1</i>	<ul style="list-style-type: none"> <li>• None or any displastic lineages.</li> <li>• One, two or three cytopenias.</li> <li>• None or any ring sideroblasts .</li> <li>• BM 5–9 % of blasts and Pb 2–4%, no Auer rods.</li> <li>• Any cytogenetics finding</li> </ul>
<i>MDS-EB-2</i>	<ul style="list-style-type: none"> <li>• None or any displastic lineages .</li> <li>• One, two or three cytopenias.</li> <li>• None or any ring sideroblasts .</li> <li>• BM 10–19 % of blasts and Pb 5–19%, or Auer rods.</li> <li>• Any cytogenetics finding.</li> </ul>
<b><i>MDS, unclassifiable (MDS-U)</i></b>	
<i>With 1% of blood blasts</i>	<ul style="list-style-type: none"> <li>• Any dysplastic lineages.</li> <li>• One, two or three cytopenias.</li> <li>• None or any ring sideroblasts .</li> <li>• BM &lt; 5% of blasts and Pb =1%, must be recorded on at least 2 separate occasions, no Auer rods.</li> <li>• Any cytogenetics finding.</li> </ul>
<i>With single lieneage dysplasia and pancytopenia</i>	<ul style="list-style-type: none"> <li>• One displastic lineage</li> <li>• Pancytopenia.</li> <li>• None or any ring sideroblasts .</li> <li>• BM &lt; 5% of blasts and Pb &lt;1%,no Auer rods.</li> <li>• Any cytogenetics finding</li> </ul>
<i>Based on defining cytogenetic abnormality</i>	<ul style="list-style-type: none"> <li>• One, two or three cytopenias.</li> <li>• Ring sideroblasts &lt;15% , in cases with the percentation &gt; = , by definition have erythroid dysplasia, and are classified as MDS-RS-SLD.]</li> <li>• Bm &lt; 5% of blasts and Pb &lt;1%, no Auer</li> </ul>

(continued)

**Table 41.3** (continued)

rods. MDS-defining abnormality.
<p><i>Refractory cytopenia of childhood</i></p> <ul style="list-style-type: none"> <li>• Any dysplastic lineage</li> <li>• One, two or three cytopenias.</li> <li>• None ring sideroblasts .</li> <li>• Bm &lt; 5% of blasts and Pb &lt; 2%.</li> <li>• Any cytogenetics finding</li> </ul>

Adapted from Arber [62]

\*Cytopenias is defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10<sup>9</sup>/L; and absolute neutrophil count <1.8 × 10<sup>9</sup>/L. Rarely MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be, 1 × 10<sup>9</sup>/L

### 41.6.1.2 Treating Cytopenias in Low Risk MDS

#### 41.6.1.2.1 Anemia

**Red Blood Cell Transfusion** Although there is not a hemoglobin value which mandates to transfusion of red blood cells, many reports show that values less than 7 g/dL are associated to fatigue, shortness of breath or related to cardiac problems. Using tissue doppler echocardiography, we detected a strong correlation between low hemoglobin levels and increased values of left ventricular end-diastolic volume, left ventricular end-systolic volume *and* left atrial volume principally when hemoglobin was less than 7 g/dL. As the most common cause of mortality in MDS patients, not related to AML transformation, is cardiac failure, we suggest that MDS patients should receive red blood cell transfusion whenever Hb value is less than 7 g/dL [63].

**Erythropoetin Stimulating Agents (ESA)** Recombinant erythropoetin (EPO) or darbopoetin is the first choice of treatment of anemia in most lower risk MDS without deletion 5q. Major favorable prognostic factors for response to ESA are low or no red blood cells transfusion dependence (<2 U/month) and baseline EPO level <500 U/L. Weekly doses of 40.000u of EPOa or 30.000 units of EPOb or 150–300 mcg of darbopoetin yield almost 60% of erythroid response when the two major prognostic factors are present. The response to ESA is an independent favorable prognostic factor for survival and is not related to AML transformation. Most responses to ESA occur within 12 weeks of treatment and close monitoring of hemoglobin level is required to avoid increases to >12 g/dL due to risk of hypertension or thrombosis. Median duration of response to ESA is approximately 2 years [64, 65].

**Lenalidomide** *Lenalidomide* is a thalidomide derivative introduced in 2004 as an immunomodulatory agent for the treatment of various cancers. Based on trials MDS003 and 004, Len (5-10 mg/day) was approved for the treatment of MDS

patients with del(5q) with RBC transfusion-dependence. Transfusion independence was achieved in up to 60% of patients with median duration of red blood cells (RBC) independence of 2–2.5 years. Of utmost importance, cytogenetic response was detected in 50–70% of cases. One very important question is what is the duration of Len treatment? But once the response is achieved (Usually after 4–6 cycles), the drug must be continued. Other potential problem with lenalidomide is the risk of secondary neoplasm or trigger AML transformation. Due to the absence of prospective randomized trials to answer these questions, retrospective studies found no excess risk of AML with lenalidomide.

More recently, Santini et al. [66] published the results of a randomized phase III trial of Lenalidomide versus placebo in low risk non-del(5q) MDS. As results, 26% of lower risk non-del(5q) MDS ineligible or refractory to ESA achieved RBC – Transfusion independence (TI). Of patients with EPO < 500U/L and prior ESA use, 35,1% achieved RBC-TI compared to 23,1% of patients with EPO > 500U/L and prior ESA use.

**ATG** Antithymocyte globulin, with or without cyclosporine, can yield an erythroid response in 25% to 40% of cases depending especially on the population treated. The most predictive markers of response are: 1- young patients; 2- low risk MDS with normal karyotype; 3- Trisomy 8 without excess blasts; 4- HLADR15 genotype; 5- a small PNH clone and Hypocellular bone marrow [67].

**Iron Chelation Therapy** Due to the absence of prospective studies related to iron chelation therapy, all the recommendations are based on retrospective studies and expert opinions. It is generally advocated starting chelation in patients with favorable prognosis who have ferritin >2500 U/L (who received at least 50/60 RBC concentrates) [68].

#### 41.6.1.2.2 Neutropenia

G-CSF and GM-CSF can improve neutropenia in 60–80% of cases, but its use have not been associated with improvement on overall survival. The recommended dosage is 300 mcg 3 times a week, but it must be remembered that the risk of AML progression has not been totally excluded [69].

#### 41.6.1.2.3 Thrombocytopenia

Platelets less than 50.000/mm<sup>3</sup> are detected in up to 30% of low risk MDS patients and severe bleeding is uncommon unless drugs interfering with hemostatic process are used. Platelets transfusion are highly immunogenic and have not long-lasting effect which precludes its use routinely. Sometimes, androgens can improve platelets count, but the response is usually transient. Eltrombopag, and oral agonist synthetic of TPO receptor have been approved for the treatment of aplastic anemia and

immune purpura and its use in lower risk MDS is being evaluated in a phase 2 phase 2 ongoing trial [70].

#### 41.6.1.3 Treating High Risk Patients

Patients with higher risk disease fall into IPSS categories of Intermediate-2 and High and R-IPSS groups of Very High, High and Intermediate (sometimes) which often correspond to WHO classification subtypes of RAEB 1 and RAEB-2. The expected median survival of these patients is usually less than 2 years. Sometimes, the correlation between WHO classification and R-IPSS is lost. For example, a patient with excess blasts but normal karyotype and limited cytopenias can live for many years while other patient with few blasts, but complex karyotype ( $\geq 3$  abnormalities at the same metaphase) and profound cytopenia may have very short survival. Although all these parameters are very important before defining MDS treatment, comorbidity must be evaluated before deciding the best option due to factors as hepatic, pulmonary, cardiac and renal disease. Della Porta et al., reported an important comorbidity index which may help the decision [64].

**Azacitidine/Decitabine** DNA methylation is a common phenomenon in advanced MDS which occurs at 5' -position of cytosine in CPG islands, resulting in silencing of gene expression. Although different mechanisms of action, both drugs induce general hypomethylation of DNA. These drugs received FDA approval based on phase 3 study in MDS patients who were randomized to the drug or supportive care. Aza was able of delaying AML transformation and significant prolongation of overall survival which was not detected in Decitabine trial. The treatment must be initiated as fast as possible because some types of higher risk MDS for example., cases with high blast counts, complex cytogenetics or  $-7/\text{del}(7q)$  may progress quickly to AML [71].

The general recommendation is a minimum of 6 cycles before concluding whether there is lack of efficacy. The standard is to continue a hypomethylating agent for as long as a response persists. Azacitidine is usually prescribed on a 7-day consecutive dosing at 75 mg/m<sup>2</sup> (SC) per day on a 28-day cycle. Treatment with Azacitidine is associated with neutropenia and thrombocytopenia. Complete blood counts should be performed as needed to monitor response and toxicity. Patients with renal impairment should be closely monitored for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys. Decitabine is usually prescribed on a 5-day consecutive dosing at 20 mg/m<sup>2</sup> per day on a 28-day cycle. Decitabine is associated with more profound cytopenias and increased chance of febrile neutropenia. Closely monitoring of hepatic and renal functions patients is extremely important when using hypomethylating agents [72].

**Bone Marrow Transplantation (BMT)** BMT is the only curative treatment for MDS. Unfortunately, this option is used in a minority of patient principally due to advanced age. Despite the lack of prospective randomized trials, BMT is recom-

mended early after diagnosis of high risk patients. Some researchers recommend pre-BMT azacitidine or decitabine therapy for patients in whom transplantation is being considered.

**Clofarabine** This purine analogue has been reported to produce response, in retrospective trials, of up to 30% of patients who failed to hypomethylating agents.

**CLAG-M (Cladribine, Cytarabine, Filgrastim and Mitoxantrone)** This schedule is considered an option for acute myeloid leukemia from antecedent MDS particularly after failure to Azacitidine.

**Rigosertib** This drug is polo- like kinase inhibitor which waits for more robust results in MDS.

**Clinical Trail** No second line therapy has demonstrated a survival advantage over any other treatment or compared to red blood cell transfusion (supportive care). Unfortunately, when MDS progress despite hypomethylating agents, the overall survival is 6 months. All these patients should be considered for clinical trials. Novel agents based on Immune Approach, such as PD1 inhibitor and CTLA-4 inhibitor are being tested with great expectation.

## Key Points

### Key Points of the Introduction

- *Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell (HSC) malignancies characterized by peripheral cytopenias caused by ineffective hematopoiesis and predisposition to acute myeloid leukemia (AML)*
- *Most of MDS patients are elderly and anemia is the most prevalent cytopenia.*
- *MDS patients present chromosomal abnormalities in up to 50% of cases.*

### Key Points of the MDS Epidemiology

- MDS is a common hematologic disorder and is encountered particularly in elderly patients
- The incidence and clinical characteristics of patients with MDS varies by geographical area, and this has been attributed to genetic or ethnic, occupational, lifestyle, and environmental factors that have not been fully elucidated.

### Key Points of the Molecular Mechanisms

- The pathophysiology and its progression to AML is multifactorial and involve cytogenetic, genetic, and epigenetic aberrations.
- Targeted sequencing of a limited number of genes can detect mutations in up to 80% of MDS cases. The most reported are *SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, *RUNX1*, *U2AF1*, *EZH2* AND *TP53*



### Key Points of the Diagnosis and Prognosis

- The diagnosis of MDS is based on clinical features, complete blood count (CBC), bone marrow analysis and cytogenetic data
- The diagnosis is one of exclusion. All other causes of cytopenia must be carefully excluded.
- Prognosis depends mainly on the marrow blast percentage, number and extent of cytopenias, cytogenetic abnormalities and presence of mutations.

### Key Points of the Pathology

- The marrow is best examined using needle biopsy and smeared preparation. Both procedures provide complementary information.
- Morphologic features of MDS include ring sideroblasts, neutrophils with only two nuclear lobes (the pseudo-Pelger-Huët anomaly) or abnormal cytoplasmic granulation, and multinucleated or small megakaryocytes with simple nuclei.
- The bone marrow study is also useful to application of other assays, such as immunohistochemistry, FISH and flow cytometry.

### Key Points of the Treatment

- ESA are the most commonly used treatment for Anemia of lower risk patients. Median duration of response to ESA is approximately 2 years
- As DNA methylation is a common phenomenon in advanced MDS, Azacitidine and Decitabine induce general hypomethylation of DNA and are usually used in Higher risk patients
- Bone marrow transplantation is the only curative treatment for MDS.

### Multiple-Choice Questions

1. Choose the item that best represents the cellularity of the bone marrow and the blood cell count in MDS.
  - (a) Hypocellular bone marrow and reduced blood cell counts
  - (b) Normocellular bone marrow and increased blood cell counts
  - (c) **Hypercellular bone marrow and reduced blood cell counts**
  - (d) Hypercellular bone marrow and increased blood cell counts
  - (e) Normocellular or hypocellular bone marrow and reduced blood cell counts.
2. An extensive diagnostic investigation is necessary to establish MDS. Which one of these is NOT included in the differential diagnosis list?
  - (a) Vitamin deficiencies (especially vitamin B12 and folate)
  - (b) Autoimmune disease
  - (c) Liver disease
  - (d) Hemolytic anemia
  - (e) **Hemophilia**

3. Myelodysplastic syndromes (MDS) comprise morphologically distinct disorders characterized by dysplastic and ineffective hematopoiesis. Which item most represents this disease?
- (a) MDS are a biologically and clinically heterogeneous group of diseases characterized by the abnormal proliferation and accumulation of immature lymphoid cells within the bone marrow and lymphoid tissues.
  - (b) MDS are a syndrome of bone marrow failure characterized by peripheral pancytopenia and marrow hypoplasia. Although the anemia is often normocytic, mild macrocytosis can also be observed in association with stress erythropoiesis and elevated fetal hemoglobin levels
  - (c) MDS are characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis.
  - (d) MDS are a stem cell disorder characterized as a panhyperplastic, malignant, and neoplastic marrow disorder. Its most prominent feature is an elevated absolute red blood cell mass because of uncontrolled red blood cell production.
  - (e) **MDS are a clonal disorder of haematopoietic stem cells which retain the ability to differentiate into end-stage cells, but do so in a disordered and ineffective manner. Consequently, the bone marrow is usually hypercellular. The progression to acute myeloid leukemia and the bone marrow failure are characteristic complications of this disease.**
4. A 62-year-old man is admitted to the hospital for excessive fatigue, fever, and bleeding. He was diagnosed with myelodysplastic syndrome 5 months ago for which he received intermittent packed red blood cell transfusions and weekly erythropoietin injections. He has not required platelet transfusions and has had no infections. His medical history is otherwise unremarkable. On physical examination, temperature is 38 °C, pulse rate is 100/min, and blood pressure is 120/80 mm Hg. Numerous ecchymoses and petechiae are visible, particularly on the extremities. There is no abdominal tenderness, splenomegaly, or lymphadenopathy. Laboratory studies indicate a hemoglobin of 4.5 g/dL (45 g/L), leukocyte count of 1100/ $\mu$ L ( $1.1 \times 10^9$ /L), and a platelet count of 7000/ $\mu$ L ( $7 \times 10^9$ /L). The peripheral blood smear shows 20% immature myeloid blasts. Which of the following is the most appropriate next step in the management of this patient?
- (a) Chemotherapy
  - (b) Plasma exchange
  - (c) **Red Blood transfusion and bone marrow aspiration.**
  - (d) Allogeneic stem cell transplantation
  - (e) Oral iron supplementation

5. A 55-year-old man comes to the physician due to excessive fatigue for 2 months, and fever for 4 days. His temperature is 39 °C, blood pressure is 120/70 mm Hg, pulse is 120/min, and respirations are 22/min. Bilateral rhonchi are heard on chest examination. He is admitted for further evaluation. Chest x-ray shows bibasilar infiltrates consistent with bronchopneumonia. Blood tests show a hemoglobin of 7,5 g/dL (75 g/L) 12,000 leukocytes/ $\mu$ L with 3% myeloid blasts. Platelet count is 45,000/ $\mu$ L. A bone marrow biopsy demonstrates hypercellular marrow. Erythroid elements with misshapen nuclei, abnormal iron-laden mitochondria (ring sideroblasts) are appreciated in peripheral and marrow blasts. Which of the following is the most likely diagnosis and the next step in the management of this patient?
- (a) Acute lymphocytic leukemia and chemotherapy.
  - (b) Myelodysplastic syndromes and allogeneic stem cell transplantation.
  - (c) Leukemoid reaction and blood transfusion.
  - (d) **Myelodysplastic syndromes and antibiotic therapy.**
  - (e) Acute lymphocytic leukemia and allogeneic stem cell transplantation.
6. Which one of these is not a feature of peripheral blood cells in myelodysplastic syndromes?
- (a) **Increased reticulocytes**
  - (b) Macrocytic red cells
  - (c) Small numbers of circulating blasts
  - (d) Neutrophils with only two nuclear lobes
  - (e) Thrombocytopenia
7. Which one of these is the most likely clinical picture in a patient with myelodysplastic syndromes associated with isolated del(5q)?
- (a) Elderly men who present with pancytopenia.
  - (b) Younger woman with unexplained isolated thrombocytopenia
  - (c) **Elderly women with mild/moderate anemia**
  - (d) Younger patients with moderate cytopenias
  - (e) Younger patients with severe cytopenia
8. Which of the following myelodysplastic syndromes is most associated with a poor prognosis in MDS?
- (a) Cytopenia(s) with 11q deletion
  - (b) Anemia with 5q deletion
  - (c) Cytopenia(s) with 12p deletion
  - (d) Cytopenia(s) with deleted 17p
  - (e) **Cytopenia(s) with TP53 mutations**
9. Myelodysplastic Syndromes has following characteristics, except:
- (a) **MDS is a congenital stem cell disorder that represent a heterogeneous group of disease.**

- (b) MDS usually refers to the presence of cytopenia in combination with a hypercellular bone marrow (BM)
  - (c) MDS exhibits dysplasia and ineffective hematopoiesis in, at least, one of myeloid cell lineages.
  - (d) The damaged stem cell in MDS retains partially the ability to differentiate into end-stage cells.
  - (e) Inherited predisposition to the disorder is evident in a third of pediatric cases, including in children with Down's syndrome, Fanconi's anemia, and neurofibromatosis.
10. The following items are all risk factors for MDS, except:
- (a) Old age, radiation treatment, alkylating agents
  - (b) Environmental exposure to benzene
  - (c) Environmental exposures to pesticides
  - (d) prior therapy, including alkylating agents and radiotherapy
  - (e) **Vitamin B12 and folate deficiency**
11. Which of the following statements regarding myelodysplastic syndromes (MDS) is correct?
- (a) Classical chemotherapy (as for AML induction) shows very important impact on overall survival.
  - (b) **The risk for the development of MDS after chemotherapy is greatest between 5 and 7 years post treatment.**
  - (c) The MCV is usually low.
  - (d) Mortality from MDS usually results from AML transformation.
  - (e) No alternative is correct
12. All of the followings causing macrocytic anemia as MDS, EXCEPT:
- (a) B12 deficiency
  - (b) Folic acid deficiency
  - (c) Liver disease
  - (d) **Thalassemia**
  - (e) Methotrexate
13. A 61-year-old man is evaluated for fatigue and diminished exercise tolerance of 2 months' duration. His medical history includes hypercholesterolemia for which he takes pravastatin. He also smoked cigarettes for 30 years before quitting 5 years ago. On physical examination, pulse rate is 90/min, and blood pressure is 140/80 mm Hg. There is no abdominal tenderness, splenomegaly, or lymphadenopathy. Laboratory studies indicate a hemoglobin of 8.6 g/dL (86 g/L), leukocyte count of 4200/ $\mu$ L, mean corpuscular volume of 96 fL, platelet count of 157,000/ $\mu$ L, and reticulocyte count of 0.5% of erythrocytes. The peripheral blood smear shows dysplastic neutrophils. On bone marrow aspirate smear, dysplastic changes in myeloid and erythroid precursors are noted, with no increase in myeloblasts and no karyotype abnormalities. He receives a trans-

fusion of red blood cells with improvement in his symptoms; however, he returns 3 weeks later with the return of his symptoms and a hemoglobin of 8.2 g/dL (82 g/L). Which of the following is the most appropriate treatment in addition to red blood cell transfusions for the patient?

- (a) Imatinib mesylate
- (b) Testosterone patch
- (c) Prednisone
- (d) **Erythropoietin**
- (e) Oral iron supplementation

14. Regarding the treatment of MDS, choose the incorrect sentence.

- (a) The goals of the therapy are to improve the cytopenia, to delay the progression to the acute leukemia and to improve the survival of the patients
- (b) **The most common cause of mortality in MDS patients is related to AML transformation.**
- (c) Median duration of response to erythropoetin stimulating agents is approximately 2 years
- (d) Bone marrow transplantation is the only curative treatment for MDS
- (e) No second line therapy has demonstrated a survival advantage over any other treatment or compared to supportive care

### Answers

1. Answer: (c) Usually, the bone marrow cellularity is normal or increased, exceeding 50% (hypercellular) in 80% of MDS patients and exhibiting dysplasia and ineffective hematopoiesis in, at least, one of myeloid cell lineages, resulting in reduced blood cell counts.
2. Answer: (e) The differential diagnosis of the MDS is made with causes of cytopenias. Hemophilia is a deficiency of coagulation factors and does not represent cytopenia.
3. Answer: (e) This item is the exact description of myelodysplastic syndrome. Item A describes acute lymphocytic leukemia, item b aplastic anemia, item c acute myeloid leukemia, and d refers to polycythemia vera.
4. Answer: (c) The next step for this patient is a blood transfusion, to stabilize their clinical state, and bone marrow evaluation to confirm the diagnosis and provide additional cytogenetic information.
5. Answer: (d) The patient presents with myelodysplastic syndromes, which constitutes a complex set of bone marrow disorders, in which at least two cell lines are affected. These conditions are characterized by cytopenias (anemia, thrombocytopenia, and/or neutropenia). The bone marrow can be hypercellular, normocellular or hypocellular. Cytopenias are due to ineffective hematopoiesis. AML transformation occurs in some cases. Many patients are asymptomatic, and the diagnosis is made on a blood sample taken for another reason. Nevertheless, some patients could present with symptoms of anemia (fatigue, shortness of breath, palpitations), thrombocytopenia (bruising, petechiae or

bleeding) or neutropenia (fever, recurrent or prolonged infections.) This patient has bronchopneumonia, so the antibiotic therapy can be established.

6. Answer: (a) Anemia, typically macrocytic and non-regenerative (therefore, there is no increase in reticulocytes), is the most common peripheral blood abnormality and occurring in approximately 80% to 85% of patients. Small numbers of circulating blasts also can be found in peripheral blood, but rarely exceeding 5%. Bilobed nucleus in neutrophils are called the pseudo-Pelger-Huët anomaly and may be present in MDS. Thrombocytopenia occurs in around 30% to 45% of MDS cases, with approximately 40% of patients found to have neutropenia at diagnosis.
7. Answer: Elderly women with mild anemia is the patient typically associated with the isolated del(5q).
8. Answer: The poor prognosis is associated with complex cytogenetic aberrations. Therefore, three or more chromosome abnormalities in a single clonal cell population), mutations in TP53, multiple cytopenias, and increased numbers of blasts have a survival times of less than 1 year.
9. Answer: (a) MDS is not a congenital problem. MDS are clonal hematopoietic stem cell (HSC) malignancies that represent a heterogeneous group characterized by ineffective hematopoiesis, dysplasia in one or more myeloid cell lineages and an increased risk of developing acute myeloid leukemia. The pathogenesis of MDS is complex and depends on the interaction between aberrant hematopoietic cells and their microenvironment
10. Answer: (e) Vitamin B12 and folate deficiency do not represent risk factors for developing syndromes. Ethnic differences and regional influences may play a role in the pathogenesis of MDS. Some data suggest that the incidence rates of MDS were highest among whites and non-Hispanics than in blacks.
11. Answer: (b) The cytogenetic features of myelodysplastic syndrome include partial or complete loss of chromosomes. The most frequent findings being deleted 5q, -7 or deleted 7q, +8, deleted 20q, and deleted 17p, but complex cytogenetic findings are common in patients with a major excess of marrow blasts or with MDS-related therapy. These cases include patients with unexplained isolated thrombocytopenia (deleted 20q), elderly women with mild anemia (deleted 5q), and younger patients with moderate cytopenias (-7 or +8), 70 confirming the clonal nature of the disease.
12. Answer: (d) All items are related to macrocytic anemia, except item d, since thalassemia presents as microcytic anemia.
13. Answer: (d) Erythropoietin therapy has been shown to improve anemia and reduce transfusion requirements.
14. Answer: (b) The most common cause of mortality in MDS patients is not related to AML transformation but is cardiac failure.

### Clinical Case

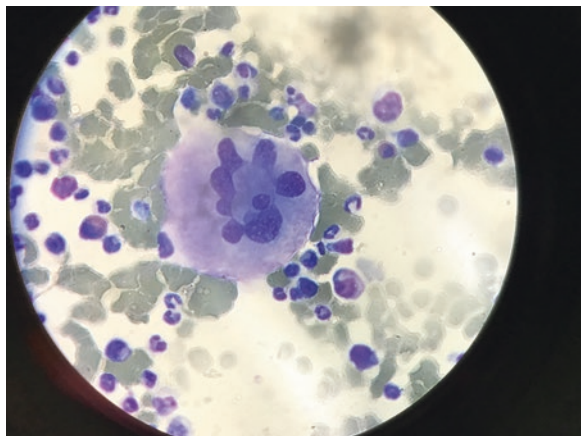
*An 80-year-old man sought for medical attention due to fatigue and dyspnea. Blood counts revealed: hemoglobin = 8.2 g/dL, MCV = 101 fl/red cell, HCM = 30 pg/red cell, white blood cell count = 6100/μL with neutrophils = 4200/L,*

lymphocytes = 600/ $\mu$ L, monocytes = 600/ $\mu$ L, eosinophils = 700/ $\mu$ L, no blast cells and platelet count of 833,000/ $\mu$ L without reticulocytosis. Vitamin (B12 and folate) and iron tests were normal and serum erythropoietin concentration was normal (38 mu/mL). The autoimmune screening with direct Coomb's test, anti-nuclear factor and rheumatoid factor (RF) due to anemia revealed a RF of 1/140. Bone marrow aspirate was normocellular with increased number of megakaryocytes with monolobulated nuclei. (Fig. 41.4) No ringed sideroblasts were found at Perl's reaction. Marrow biopsy was normocellular with multiple megakaryocytes with monolobulated nuclei, fibrosis grade II and no dysplasia in other series. Bone marrow karyotype showed: 46, XY, del(5q)(q15q33)[4]/46, XY[16]. The diagnosis of 5q- syndrome by World Health Organization (WHO) was established and by the Revised International Prognostic Scoring System Risk Group (IPSS-R) was classified as low risk. The patient is red blood cell transfusion-dependent.

### Discussion

Van den Berghe et al, in 1974, reported a syndrome that occurred primarily in elderly women with macrocytic anemia, normal or elevated platelets, increased number of megakaryocytes with monolobulated nuclei and isolated del(5q) cytogenetic abnormality. The WHO classification system included this syndrome as a subtype of MDS named the 5q- syndrome. This syndrome occurs more frequently in older women (male/female ratio = 0.5) and the most common symptoms are related to refractory anemia. The deletion 5q is interstitial, with the breakpoints that are most frequently cited being 5q31-q33, although some heterogeneity may exist, ranging from bands 5q12 to 5q35. Peripheral blood usually presents macrocytic anemia with elevated or normal platelet count and the bone marrow smear is normocellular or hypercellular with monolobulated megakaryocytes. Patients with the 5q- syndrome experience a relative benign disease course extending over several years and transformation into leukemia is not so rare. Autoimmune manifestations (AIM) as vasculitis, pyoderma gangrenosum, hemolytic anemia, immune thrombocytopenia, rheumatoid arthritis as well as positive anti-nuclear factor and rheumatoid factor

**Fig. 41.4** Marrow core biopsy showing multiple megakaryocytes with monolobulated nuclei



*have been reported in 13–30% of MDS patients. In a few cases, cytogenetics abnormalities are reported, but the relation between these phenomena is unknown.*

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**Part IV**  
**Palliative Care and Supportive Care**

# Chapter 42

## Metabolic Disturbance



**Pamela Carvalho Muniz, Mayndra Mychelle Landgraf, Fernando Silva Picon, Hakaru Tadokoro, Ramon Andrade De Mello, and Michelle Samora de Almeida**

**Abstract** As specific cancer treatments evolved, our ability to anticipate side effects and prevent them has also been refined. Prophylaxis allows us to avoid numerous metabolic alterations, but it is still a frightening terrain in view of its clinical consequences. Knowing deeply the diagnostic steps and their management is of fundamental importance in the daily routine of the caregiver (Lawrence TS, Rosenberg SA: DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. Lippincott Williams & Wilkins, Philadelphia, 2015).

**Keywords** Palliative care · Supportive care · Cancer

### 42.1 Introduction

As specific cancer treatments evolved, our ability to anticipate side effects and prevent them has also been refined. Prophylaxis allows us to avoid numerous metabolic alterations, but it is still a frightening terrain in view of its clinical consequences.

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Knowing deeply the diagnostic steps and their management is of fundamental importance in the daily routine of the caregiver [1].

This chapter aims to discuss the main oncological metabolic emergencies and their clinical management, to mention: hypercalcemia of malignancy (HM), tumor lysis syndrome (TLS) and hyponatremia.

## 42.2 Hipercalcemia of Malignancy

The diagnosis of hypercalcemia in the hospital environment, mainly in intensive care, is routine. Although a broad etiological spectrum is involved, the differential diagnosis generally relies on primary hyperparathyroidism and hypercalcemia of malignancy [2]. In cancer patients it is not an infrequent complication, especially in those with advanced disease, occurring in almost 30% of them [3].

Alone, the diagnosis of hypercalcemia confers a worse prognosis to the patient, which in numbers translates to a mortality rate of 50% in 30 days after the diagnosis of this complication [4].

As for the cancer subtypes most associated with hypercalcemia, in general, we can mention: carcinomas of breast, lung, head and neck, kidney and multiple myeloma [1].

More than one mechanism is involved in the etiology of hypercalcemia of malignancy, among them:

- (a) **PTH-related peptide production (PTHrP)**, also called humoral malignant hypercalcemia, whose action is similar to PTH, which in this scenario will present with low PTH serum levels, representing 80% of hypercalcemia of malignancy and in general not associated with de facto bone metastases;
- (b) **local osteolytic**: increased bone resorption resulting from the activation of osteoclasts by substances from the tumor cells themselves. In this case, there is bone metastases or multiple myeloma, which corresponds to approximately 20% of the cases;
- (c) **production of calcitriol**, caused mainly by some subtypes of lymphomas, corresponds to about 1% of the hypercalcemia of the malignancy, where there is production of calcitriol by the tumor cells causing increase of renal resorption and gastrointestinal absorption of calcium;
- (d) **ectopic hyperparathyroidism**, when PTH is elevated (confounder with primary hyperparathyroidism) due to the paraneoplastic production of PTH, an extremely rare variant [4, 5].

Although the focus is on the malignant causes of hypercalcemia, we must not forget other causes, which should be systematically excluded in the diagnostic investigation, among them: parathyroid-dependent hypercalcemia, primary hyperparathyroidism, tertiary hyperparathyroidism, familial hypocalciuric hypercalcemia, lithium, granulomatous diseases, hyperthyroidism, adrenal insufficiency, medications such as thiazide diuretics, vitamin D and calcium (milk-alkali syndrome), vitamin A, teriparatide, and immobilization [2].

The laboratory measurement of serum calcium or serum calcium corrected by albumin is necessary for the diagnosis of hypercalcemia. Clinically, the symptoms

include lethargy, mental confusion, constipation, polyuria, polydipsia or, on the contrary, it can be an asymptomatic laboratory change [6].

Immediate reversal of hypercalcemia with the appropriate therapy must occur as soon as the diagnosis is made, although not with the precise etiology. It is necessary to keep in mind the targets of the treatment, which consist of reducing calcium, correcting dehydration and reducing osteoclastic activity [7].

The first therapeutic course is the administration of intravenous fluids vigorously. Saline solution replacement is indicated and the goal is to offer 3–6 liters in the first 24 h, depending on the associated comorbidities and degree of dehydration [8].

The previously recommended use of loop diuretics is now restricted to patients with volume-limiting cardiac dysfunction or oliguric renal insufficiency, because despite increasing calcium excretion, it can occur with innumerable other metabolic disorders besides worsening hypovolemia [9, 10].

Another fundamental pillar in the therapeutic management of hypercalcemia is the administration of inhibitor agents of bone resorption, the bisphosphonates, which ultimately lead to osteoclast apoptosis [11]. Pamidronate is a therapeutic option (90 mg dose infused over 2 h) but it is less potent than zoledronic acid (4 mg intravenously in 15 min) [12]. Pamidronate is a plausible alternative for patients with creatinine clearance less than 30 mL/min when zoledronic acid is not recommended [5].

Calcitonin, a hormone produced by parafollicular cells that reduces calcium by inhibiting osteoclasts, can be used as a hypocalcemic agent at an initial dose of 4 U/kg intramuscularly or subcutaneously every 12 h until the onset of the bisphosphonate effect. Its initial effect begins in approximately 4–6 h but one should always pay attention to the risk of tachyphylaxis (in 3 days) [9].

By reducing the synthesis of 1,25 dihydroxyvitamin D, glucocorticoids can be used in cases of hematological diseases such as lymphomas and myelomas [13].

Another option is denosumab, a humanized monoclonal antibody that decreases osteoclast activity and it is not excreted via the kidneys, which can be used if refractory to bisphosphonates at a dose of 120 mg subcutaneously [14].

In patients who have undergone the aforementioned treatments and still maintain severe hypercalcemia, they should be evaluated for the possibility of performing hemodialysis [14].

### 42.3 Tumor Lysis Syndrome

Most commonly seen in hematological neoplasms and solid neoplasms highly responsive to treatment, where the rate of cell proliferation is high, tumor lysis syndrome (TLS) represents a potentially lethal but preventable and treatable oncological emergency if correctly diagnosed [6].

In response to chemotherapy or spontaneously, the cells release their contents into the bloodstream by forming tumor lysis and causing hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia [15].

**Table 42.1** Cairo-Bishop definition of laboratory tumor lysis syndrome for adults

Variable	Value	Change from baseline value
Uric acid	≥8 mg/dL (476 mmol/L)	25% increase
Potassium	≥6.0 mEq/L (or 6 mmol/L)	25% increase
Phosphorus	≥4.5 mg/dL (1.45 mmol/L) for adults and ≥6.5 mg/dL (2.1 mmol/L) for children	25% increase
Calcium	≤7 mg/dL (1.75 mmol/L)	25% increase

Adapted from Cairo et al. [17] and Mirrakhimov AE et al. [16]

The severity of the syndrome is due to the clinical consequences that may occur, such as: arrhythmias, central nervous system toxicity, renal failure and even death [16].

The tables below show a more widely used classification of TLS (Tables 42.1 and 42.2).

High-risk neoplasms for the development of tumor lysis, such as Burkitt's lymphoma, acute lymphoblastic leukemia, and acute myeloid leukemia, should receive prophylactic measures for the syndrome.

Vigilant measures with serial examinations should be adopted. Hydration is the most effective measure. Excess uric acid can lead to precipitation in the renal tubules, causing acute renal injury. Hyperphosphatemia can lead to deposition of calcium phosphate, also causing kidney damage. Therefore, adequate hydration increases renal perfusion and leads to increased urinary flow, reducing risks of precipitation. Evidences of prophylactic urinary alkalization with intravenous bicarbonate solutions are controversial and should not be routinely used. Diuretics are contraindicated in patients with hypovolemia and should be used with caution in the other patients. Patients with established renal impairment should receive evaluation from a nephrologist and dialysis therapy should not be delayed [18–20].

Allopurinol, a competitive inhibitor of xanthine oxidase, blocks the conversion of purine metabolites into uric acid. Its prophylactic use in high-risk patients is associated with fewer obstructive uropathies and TLS [21].

In established TLS situations, the initial approach should involve careful electrolyte analysis and cardiac monitoring. Potassium and calcium disturbances may cause cardiac arrhythmias, so their correction according to specific guidelines should be readily obtained [22].

Hydration is the key measure in the treatment of TLS. According to specific recommendations, the goal for urine output in adults is 80–100 mL/m<sup>2</sup>/hr. Urine-specific gravity should be monitored and maintained below 1.010 [19].

Allopurinol should be initiated at a dose of 100 mg/m<sup>2</sup> orally every 8 h or 200–400 mg/m<sup>2</sup> intravenously per day. In patients with renal impairment, a 50% dose reduction is recommended. The recombinant form of urate oxidase, rasburicase, converts uric acid to allantoin. The main advantage over allopurinol is the speed of the effect [21]. Rasburicase decreases uric acid while allopurinol reduces the formation of new uric acid, which has no immediate effect. Recommended dose is 0.10–0.2 mg/kg daily and should be adjusted according to the evolution of uric acid values. Rasburicase is contraindicated in patients with a proven G6PD deficiency [18, 19].



**Table 42.2** Cairo-Bishop grading of clinical tumor lysis syndrome for adults

Variable	Grade 0	Grade I	Grade II	Grade III	Grade IV	Grade V
Creatinine	None	1.5 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	>1.5–3.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	>3.0–6.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	>6.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	Death
Cardiac arrhythmia	None	Intervention not indicated	Nonurgent medical intervention indicated. Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator). Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Life-threatening (e.g., arrhythmia associated with HF, hypotension, syncope, shock). Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Death
Seizures	None	–	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

Adapted from Cairo et al. [17] and Mirrakhimov AE et al. [16]

## 42.4 Hyponatremia

Hyponatremia is a metabolic disorder commonly found in cancer patients, defined as serum sodium  $<130$  mEq/L. The incidence is 3.7% in malignancies, reaching 47% of patients hospitalized with cancer [23, 24].

Major clinical manifestations include nonspecific symptoms such as anorexia, nausea and asthenia, as well as neurological symptoms such as lowering of consciousness level, generalized hypotonia, and seizures [1].

As major causes of hyponatremia in cancer patients we have:

- (a) **Hypovolemia** due to gastrointestinal or renal losses, poor oral intake and depletion of the effective circulating volume (such as ascites, heart failure or cirrhosis) [25]
- (b) **Syndrome of inappropriate antidiuretic hormone (SIADH)**. SIADH may be the result of an ectopic production of the antidiuretic hormone (ADH) by tumors such as small cell lung cancer, head and neck tumors, and brain tumors. It may also be found in patients receiving high intravenous doses of cyclophosphamide and vinca alkaloids such as vincristine and vinblastine [26]
- (c) **Pseudohyponatremia**: May occur in patients with Multiple Myeloma and hyperproteinemia. The plasma osmolality of these patients is normal and pseudohyponatremia occurs as a consequence of how serum sodium is measured. The most commonly used method for quantifying serum sodium concentration is ion-selective electrode (ISE) potentiometry and it is believed that osmotic effect of paraproteins interfere with the measurement. Flame emission spectroscopy is a laboratory method that clarifies the diagnostic doubt [27]

Plasma osmolality, under normal conditions, ranges from 280 to 295 mOsm/kg, and is mainly regulated through three mechanisms: thirst perception, control of fluid loss by the kidney through ADH and regulation of renal sodium excretion through the atrial natriuretic peptide (ANP) and the renin-angiotensin system [1].

In patients with cancer, SIADH is characterized as a paraneoplastic syndrome and is defined as dilutional hyponatraemia with high urine sodium excretion. It occurs due to dysregulation at the threshold of plasma osmolality, causing ADH secretion even with low osmolality. ADH can be produced in the hypothalamus or in its ectopic source [25, 26].

Two other known mechanisms of hyponatremia are the syndrome of inappropriate atrial natriuretic peptide (SIANP) and cerebral salt loss syndrome (CSWS). ANP is produced and released by atrial myocytes binding to receptors that increase renal sodium excretion [28]. CSWS is characterized by brain injury and high urinary sodium excretion associated with extracellular volume depletion.

It is important to make the correct diagnosis to implement the appropriate treatment.

Treatment is based on the cause and hyponatremia secondary to gastrointestinal and renal losses and reduced intake should first be ruled out.

If hyponatremia is secondary to chemotherapeutics, treatment consists of suspending them [1].

When these causes are excluded, the presumptive diagnosis is that of SIADH, whose treatment is to restore serum sodium and osmolality. The speed of correction will depend on the symptoms presented and the time of installation. If chronic, the symptomatology tends to be low and the correction should be performed for a few days. If acute and symptomatic the correction may be more aggressive.

In most cases hyponatremia is mild and can be managed with water restriction and oral saline.

In symptomatic cases, the replacement should be performed with intravenous saline and diuretics such as furosemide. If hyponatremia is worsening or does not improve within 72–96 h, investigation with ADH and ANP dosing to differentiate between SIADH and SIANP should be continued. Management of SIANP may be more difficult due to the persistence of hyponatremia after water restriction [1].

Other options for refractory hyponatremia are the aquaretic agents and the arginine vasopressin (AVP) receptor antagonists, which have proved to be safe and effective [29].

### Questions

1. **A 50-year-old man diagnosed with metastatic squamous cell carcinoma of the oropharynx presents with mental confusion, constipation, and vomiting. Laboratory tests of admission showed sodium: 148 mEq/L, potassium of 4.5 mEq/L, Calcium of 13.7 mg/dL. What is the most appropriate initial propaedeutic?**
  - (a) Intravenous fluids and bisphosphonate
  - (b) **Intravenous fluids, bisphosphonate and calcitonin**
  - (c) Vigorous intravenous fluids
  - (d) Intravenous fluids, bisphosphonate, calcitonin and hemodialysis
2. **Regarding the Hipercalcemia of Malignancy, it is incorrect to state that:**
  - (a) It is a frequent complication in cancer patients, especially in inpatients.
  - (b) Carcinomas of breast, lung, head and neck, kidney and multiple myeloma are the most common neoplasias associated with this condition;
  - (c) Hyperparathyroidism, hyperthyroidism and medications are possible differential diagnoses and should be discarded in these patients;
  - (d) **Despite the severity, hypercalcemia is easily reversible and provides better prognosis than those who do not have this condition;**
3. **Check the alternative that contains a correct statement about Hypercalcemia of Malignancy:**
  - (a) Diuretics are recommended to increase urine output and are widely used;
  - (b) **Lethargy, mental confusion, constipation, polyuria, and polydipsia are common symptoms in this condition. However, there are patients who are asymptomatic;**

- (c) Pamidronate is the most potent bisphosphonate and is the gold standard for treatment;
  - (d) Calcitonin is a treatment option, but its main problem is the time of onset of the effect, which can take days.
4. **Regarding the Tumor Lysis Syndrome (TLS), it is INCORRECT to state:**
- (a) It is a more frequent complication in hematological malignancies than in solid tumors;
  - (b) There are cases of spontaneous TLS;
  - (c) Arrhythmias can occur and hydroelectrolytic disorders are the main cause;
  - (d) **Hypercalcemia and hyperphosphatemia are the main disorders of calcium and phosphorus, respectively;**
5. **A 44-year-old man performed the first cycle of chemotherapy for a Burkitt's Lymphoma. Family members brought him to the hospital because of a mental confusion and lethargy. Heart rate of 118 bpm, respiratory rate of 28 and blood pressure of  $100 \times 60$  mmHg. Laboratory exams show: Na = 145, K = 7.5, Ca = 7.5 (8.5–10.2 mg/dL), P = 4.9 (2.5–4.5 mg/dL) and Uric Acid = 11 (2.5–7.0 mg/dL). Regarding this case, mark the only incorrect medical conduct:**
- (a) **Hypotonic solution;**
  - (b) Calcium gluconate is recommended for this situation;
  - (c) Nebulization with beta agonists;
  - (d) Rasburicase;
6. **Taking into account the previous case, more examinations were requested. Creatinine = 2.3 mg/dL, BUN = 100 (16–40 mg/dL), HCO<sub>3</sub> = 16 (22–26 mEq/L), pH = 7.27 (7.35–7.45) and pCO<sub>2</sub> = 26 (35–45 mmHg). Which of the alternatives is correct?**
- (a) It is a respiratory acidosis caused by patient anxiety;
  - (b) **Renal hypoperfusion is occurring in this patient;**
  - (c) This is renal failure due to post-renal obstruction;
  - (d) Diuretic stimulation with furosemide should be attempted;
7. **Still talking about the case of question 5, point out the INCORRECT alternative about the management of hyperuricemia:**
- (a) Hydration is able to reduce uric acid levels in this patient;
  - (b) Allopurinol decreases the formation of endogenous uric acid and should be used;
  - (c) Studies on the prophylactic use of allopurinol have shown benefits in obstructive uropathy and tumor lysis syndrome. Because it is a high-risk tumor, prophylaxis should be started in the first cycle of chemotherapy
  - (d) **Rasburicase is a new agent for the treatment of hyperuricemia. Among its mechanisms of action is the reduction of absorption of uric acid from the diet.**

8. **Concerning the treatment of the Tumor Lysis Syndrome (TLS), it is correct to state:**
- (a) Prophylactic urinary alkalinization with intravenous bicarbonate leads to a lower deposition of uric acid and should be used;
  - (b) High doses of furosemide may be used to promote urine output;
  - (c) **Rasburicase should be avoided in G6PD deficiency;**
  - (d) Allopurinol leads to degradation of uric acid in allantoin;
9. **Tumor Lysis Syndrome can cause hyperuricemia. Regarding the treatment and prevention of this condition, mark the only correct alternative:**
- (a) There is no renal correction of allopurinol dose;
  - (b) Allopurinol prevents the conversion of pyrimidine metabolites to uric acid;
  - (c) Urinary precipitation of uric acid can lead to acute renal failure, requiring alcalinization and IV fluids;
  - (d) **Rasburicase causes immediate reductions of uric acid, being an important advantage over allopurinol;**
10. **Hyponatremia is a condition that is related to neoplasms. Check the correct alternative:**
- (a) Hyponatremia is defined as urinary sodium value below 130 mEq/L;
  - (b) Syndrome of inappropriate antidiuretic hormone (SIADH) is associated with hypovolemia;
  - (c) Sodium must be rapidly corrected for reversion of symptoms;
  - (d) **Hyponatremia is often asymptomatic and it is necessary to verify if it is not a pseudohyponatremia;**
11. **Which malignant neoplasm is most associated with hyponatremia?**
- (a) **Small cell lung cancer**
  - (b) Thymic cancer
  - (c) Breast cancer
  - (d) Colon cancer
12. **Which of the following chemotherapies does not cause hyponatremia?**
- (a) Cyclophosphamide
  - (b) Vinblastine
  - (c) Vincristine
  - (d) **Doxorubicin**
13. **What are the main measures in the treatment of chronic hyponatremia?**
- (a) **Water restriction and increased oral salt intake**
  - (b) Diuretics and intravenous saline replacement
  - (c) Water restriction and aquaretic agents
  - (d) Aquaretic agents and increased oral salt intake

14. **What are the main causes of hyponatremia in patients with cancer?**

- (a) Gastrointestinal loss
- (b) Poor oral intake
- (c) SIADH
- (d) **All above**

15. **On hypercalcemia of malignancy it is incorrect to state:**

- (a) **The symptoms of hypercalcemia depend mainly on the serum calcium levels having no relation with the speed of installation.**
- (b) Dehydration and renal failure may occur when serum calcium is  $>14.0$  ng/dl – and clinically patients may present with changes in mental status, coma, and death.
- (c) Symptoms of mild and moderate hypercalcemia include polyuria, polydipsia, nausea, mental confusion, vomiting, abdominal pain.
- (d) Since patients are invariably dehydrated the initial treatment of hypercalcemia involves aggressive resuscitation with 0.9% saline fluids or other intravenous crystalloids without calcium.

**Commentaries**

1. Calcitonin is the agent that will act more quickly to reduce calcemia, in view of severe hypercalcemia. An essential pillar of the treatment of malignant hypercalcemia is endovenous hydration. The use of bisphosphonates is also indicated.
2. All alternatives contain correct statements except for letter D. Although potentially reversible, it is known that patients with hypercalcemia of malignancy have a worse prognosis than those with normal calcium.
3. The role of diuretics is quite controversial and is not recommended by some authors. Alternative B is correct. The listed symptoms are possible in hypercalcemia of malignancy. However, most patients are asymptomatic. Pamidronate is less potent than zoledronic acid. Alternative D is incorrect because the effect of calcitonin does not take days.
4. Alternatives A, B and C bring concepts about Tumor Lysis Syndrome and are all correct. Alternative D is incorrect because hypocalcemia is the most common calcium disorder and not hypercalcemia. It is believed that excess phosphorus released in tumor lysis binds to calcium, leading to a reduction in serum calcium.
5. Initial hydration should always be done initially with isotonic saline solutions despite plasma sodium levels (alternative A incorrect). Since it is a symptomatic hypocalcemia, calcium replacement should be applied with calcium gluconate. The patient has high plasma potassium and nebulization with beta agonists is a valid strategy to try to reduce it. Rasburicase can be used to correct the uric acid levels of this patient.
6. The patient does not have respiratory acidosis and the anxiety is not interfering with his clinical condition (alternative A is absurd). Hypotension of this patient is causing renal hypoperfusion, which explains the increase in BUN and

- creatinine (alternative B is correct). The cause of renal failure is pre-renal and we have no evidence to consider post-renal obstruction. Diuretic stimulation with furosemide should not be attempted without proper hydration before.
7. Rasburicase is a recombinant form of urate oxidase that converts uric acid to allantoin. There is no information that it interferes with the intestinal absorption of uric acid (alternative D is correct). The other alternatives make correct statements.
  8. Prophylactic urinary alkalization with intravenous bicarbonate is still a rather controversial measure in the literature. The use of high doses of furosemide to stimulate diuresis is not completely accepted and there is no reason to assume that it is a standard treatment. Rasburicase should be avoided in G6PD deficiency due to the risks of toxicity (alternative C is correct). Allopurinol is not able to decrease the levels of uric acid already formed. Its action is in reducing the synthesis of endogenous uric acid. The degradation of uric acid into allantoin is an effect of rasburicase.
  9. Allopurinol should have hepatic correction. It decreases the endogenous synthesis of uric acid by decreasing the conversion of pyrimidine metabolites to uric acid. One of the most feared complications of hyperuricemia is renal failure, which is multi-factorial. Intra-renal deposition of uric acid crystals is one of the causes of renal dysfunction. Alternative D is correct. When compared to allopurinol, rasburicase has the advantage of promoting reductions in plasma uric acid levels faster.
  10. The definition of hyponatremia of alternative A is correct. Syndrome of inappropriate antidiuretic hormone (SIADH) may occur in patients with normal blood volume, not necessarily related to hypovolemia. Rapid corrections of sodium levels can lead to complications, especially in patients with chronic alterations. Therefore, quick conversions should not be the goal. Hyponatremia may be asymptomatic, especially in chronic patients. Pseudo-hyponatremia should be discarded when we have a hyponatremia seen in medical exams.
  11. One cause of hyponatremia, like SIADH may be the result of an ectopic production of the antidiuretic hormone (ADH) by tumors such as small cell lung cancer, head and neck tumors, and brain tumors.
  12. In patients with hyponatremia related to SIADH, it may also be found in patients receiving high intravenous doses of cyclophosphamide and vinca alkaloids such as vincristine and vinblastine.
  13. In most cases hyponatremia is mild and can be managed with water restriction and oral saline.
  14. In patient with cancer, gastrointestinal loss, poor oral intake, SIADH, cerebral salt loss syndrome are important causes of hyponatremia.
  15. Just as serum calcium levels dictate the severity of the metabolic disorder, so does your installation speed. The more acute, the more serious.

### Clinical Case and Commented Questions

X. T. D. B.; 23 years old, a student with no previous comorbidities, is admitted to the emergency room due to nausea, vomiting, drowsiness, weight loss of 10 kg and palpable mass in the abdominal region.

During the initial investigation detected in laboratory exams the presence of hypercalcemia (Ca: 17 mg/dL) and acute renal failure (Cr: 2.5 mg/dL). An additional laboratory was requested that showed hyperuricemia (AU: 20.6 mg/dL) and hyperphosphatemia (P: 5.2 mg/dL). In CT scans, an expansive lesion measuring 5.4 x 3.7 cm was found in the perineal region extending to the pelvis, compromising the right ischium associated with bilateral pulmonary nodules up to 1.5 cm and multiple bone lesions in the axial skeleton.

After diagnosis of tumor lysis and hypercalcemia associated with malignancy was initiated hydration (100 ml/m<sup>2</sup>/h), allopurinol 100 mg/m<sup>2</sup> orally every 8 h, calcitonin 300 U IM and pamidronate 90 mg in 120 min.

The patient evolved with symptomatic improvement in the first 24 h. After two days, the malignant neoplasm was diagnosed as Rhabdomyosarcoma and started specific treatment for the disease with good tolerance.

After five days of admission, the patient was asymptomatic and with normal laboratory tests (AU: 6.3 mg/dL, Ca: 9.2 mg/dL, P: 2.4 mg/dL and Cr: 0.8 mg/dL).

At the moment, he is in first-line treatment for 7 months with good tolerance and asymptomatic.

According to the guidelines, calcitonin is the agent that will act more quickly to reduce calcemia, in view of severe hypercalcemia. Another essential pillars of the treatment of malignant hypercalcemia are vigorous intravenous hydration and bisphosphonates.

### Questions

1. What are the diagnostic criteria for Tumor Lysis Syndrome present in the clinical case above?
2. What measures have been started to manage hypercalcemia of malignancy?
3. What are the therapeutic measures of fundamental importance for the management of tumor lysis syndrome?

### Comments

1. The tumor lysis syndrome presents with hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia. In the clinical case, according to the Cairo-Bishop definition of laboratory tumor lysis syndrome for adults we could detect hyperuricemia (AU: 20.6 mg/dL) and hyperphosphatemia (P: 5.2 mg/dL). Hypercalcemia here is due to hypercalcemia of malignancy, also present.
2. After diagnosis of hypercalcemia of malignancy was initiated hydration (100 ml/m<sup>2</sup>/h), calcitonin 300 U IM and pamidronate 90 mg in 120 min. The first therapeutic course is the administration of intravenous fluids vigorously. Calcitonin can be used as a hypocalcemic agent at an initial dose of 4 U/kg intramuscularly or subcutaneously every 12 h until the onset of the bisphosphonate effect. Pamidronate is a therapeutic option (90 mg dose infused over 2 h) but it is less potent than zoledronic acid (4 mg intravenously in 15 min).



3. After diagnosis of tumor lysis was initiated hydration (100 ml/m<sup>2</sup>/h), allopurinol 100 mg/m<sup>2</sup> orally every 8 h. Hydration is the most effective measure and the key measure in the treatment of TLS. Allopurinol, a competitive inhibitor of xanthine oxidase, blocks the conversion of purine metabolites into uric acid. Its prophylactic use in high-risk patients is associated with fewer obstructive uropathies and TLS.

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# Chapter 43

## Neoplastic Epidural Spinal Cord Compression



**Andrea Morais Borges, Adrialdo José Santos, Hakaru Tadokoro, and Ramon Andrade De Mello**

**Abstract** Spinal metastasis is the most common type of neoplasia, where in autopsy investigations it has been shown that up to 70% of cancer patients present it (Klimo P Jr, Schmidt MH: *Oncologist* 9(2):188–196, 2004; Chamberlain MC: *Hematol Oncol Clin North Am* 26(4):917–931, 2012). Compression of the spinal cord, an extremely devastating scenario, and mainly caused by spinal metastases with extension to the epidural space, directly affects the quality of life of cancer patients, reaching 5–10% of patients with metastatic cancer (Helweg-Larsen S, Sorensen PS, Kreiner S: *Int J Radiat Oncol Biol Phys* 46:1163–1169, 2000). The thoracic and lumbar spine are the most commonly affected (Klimo P Jr, Schmidt MH: *Oncologist* 9(2):188–196, 2004).

**Keywords** Spinal cord compression · Oncologic emergency · Pain control

### 43.1 Introduction

Spinal metastasis is the most common type of neoplasia, where in autopsy investigations it has been shown that up to 70% of cancer patients present it [1, 2]. Compression of the spinal cord, an extremely devastating scenario, and mainly

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caused by spinal metastases with extension to the epidural space, directly affects the quality of life of cancer patients, reaching 5–10% of patients with metastatic cancer [3]. The thoracic and lumbar spine are the most commonly affected [1]. Pain is the most common initial symptom, and as the spinal cord injury progresses, the central nervous system (CNS) is compromised, and if left untreated the spinal cord injury becomes irreversible [4]. The management of neoplastic disease of the spine has changed significantly during the last decades. Advances include improvements in radiotherapy and chemotherapy therapies, and research has been improving our understanding of tumor biomechanics in the spine. Increasingly, the need for a surgical approach is diminishing, but in the scenario of tumor instability it is still the main therapy [5].

## 43.2 Epidemiology

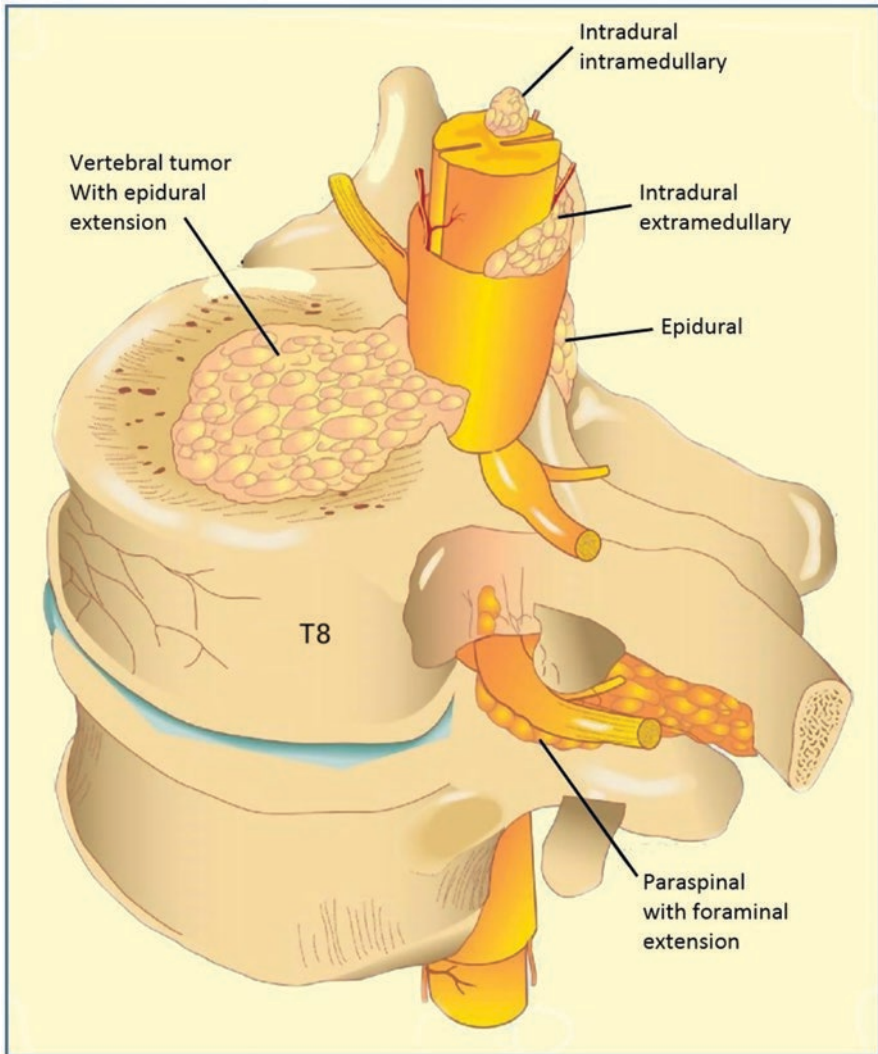
More than 1.4 million new cases of cancer are diagnosed annually in the United States [6, 7]. Neoplastic Epidural Spinal Cord Compression (NESCC) affects on average 10–15% of patients diagnosed with spinal metastases [8]. The majority of patients with NESCC are over 50 years of age, however, cumulative incidence decreases over the years [4, 9]. The mean interval between cancer diagnosis and NESCC manifestation ranges from 6 to 12.5 months [4].

The most common sources of NESCC are breast cancer (20%), lung cancer (13%), lymphoma (11%) and prostate cancer (9%) [2, 10]. Fifteen percent of all NESCC is located in the cervical spine, 68% occurs in the thoracic spine and 16% in the lumbar spine [2]. The over-representation of the thoracic involvement reflects the large thoracic spine size, as well as the comparatively small diameter of the thoracic spinal canal. Breast and lung carcinomas tend to metastasize to the cervical and thoracic vertebrae, tumors of the prostate, colon, and pelvic areas have a predilection for the lumbar spine and sacral region [7, 8].

NESCC as a primary manifestation of a malignant neoplasm is more common in non-Hodgkin's lymphoma, myeloma, and lung cancer (especially the small cell variant), and such a characteristic is rarely seen in breast cancer, which tends to be later [11]. In the pediatric population, NESCC occurs, as an initial manifestation, more frequently than in adults, and includes neuroblastoma and sarcomas, followed by germ cell tumors and lymphoma [4, 12].

## 43.3 Pathophysiology

Figure 43.1 shows the anatomy of the spinal cord, associated structures and the location of metastatic lesions in these areas. These lesions usually first invade the epidural space, most often as direct extension of metastatic disease from the vertebral body.



**Fig. 43.1** Locations of metastatic lesions of the spine

Several factors contribute to the high incidence of metastatic deposition and growth in the vertebrae. These include the presence of the Batson epidural venous plexus with bidirectional flow and direct communication with the thoracic and pelvic venous system. In addition, the vertebrae contain vascular marrow (red marrow) unlike the bones of the peripheral skeleton [2]. RANKL (the main stimulator of bone resorption and formation / activation of osteoclasts) is overexpressed in bone metastases, whereas osteoprotegerin (OPG) serum levels (negatively regulate bone resorption by inhibition of osteoclasts) are decreased in patients with metastases bone [2, 13].

Pathologically, 3 stages of the ESCC are observed. Initially, axonal and white cord edema of the medullary cord is observed with preservation of the medullary vascular flow. Then mechanical compression of the marrow is increased due to worsening white matter edema and initial changes in vascular flow are seen. At the later stage, hemorrhages and necrosis of white matter are observed [14].

NESCC can be produced by direct mechanical compression of the medullary canal or root of the nerve by the tumor itself; by disruption of the vascular supply to the spinal cord by the tumor; or by direct vertebral compression or collapse due to pathological fracture (spine instability) [15, 16].

### 43.4 Clinical Evaluation

The most common presenting symptom in patients with metastases involving the axial skeleton is the back pain [4, 7, 17, 18]. This symptom is usually neglected due to high incidence of musculoskeletal pain not a carcinogen in common society. However, any back pain in a patient with cancer known to frequently seed to spine or epidural space should be considered of metastatic origin until proven otherwise.

Pain ensues when the richly innervated periosteum is involved (periosteal stretching and/or a local inflammatory process stimulates the pain fibers within the spinal periosteum). Three classic pain syndromes affect patients with spinal metastases: local, mechanical, and radicular pain [7]. Local pain is usually described by patients as a persistent. Mechanical pain is exacerbated by movement, activity, or the Valsalva maneuver. Radicular pain in the thoracic region is usually bilateral, whereas cervical and lumbar radiculopathies are unilateral [19]. Referred pain may mimic a radiculopathy. Especially with intraneural tumor spread, neuropathic features (allodynia, hyperpathia, hyperalgesia) may predominate [4].

Motor dysfunction is the second most common presenting complaint of patients with vertebral metastases. Occurs before sensory disturbance [20]. Typical early complaints are difficulty raising your legs, climbing stairs or getting up from a chair, by sensation of “heavy” legs [17, 18]. Due to the majority of the NESCC begin in the thoracic spine, most patients present with a paraparesis. Epidural progression of metastases to the upper lumbar spine results in conus medullaris syndrome with distal lower extremity weakness, saddle paresthesia, and bladder or bowel dysfunction (autonomic symptoms).

Thoracic pain is less common than is pain originating from the cervical and lumbar regions, where degenerative disease is the more common precipitating cause of pain; thus pain in the thoracic region should raise a level of suspicion for to be oncologic.

Sensory disturbances typically occur in correlation with motor dysfunction both in location and time of onset. The level of hypesthesia is usually two to three segments below the metastatic lesion [18]. It is important to carry out a thorough questioning of patients with spinal metastases due to the neglect of early symptoms such as nocturia, pollakisuria, urinary loss, mild limb paresthesia or in band.

The table below (Table 43.1) summarizes the spinal cord syndromes according to their topography and symptoms.

**Table 43.1** Topographic spinal cord syndromes

Clinical features	Spinal cord (above the conus medullaris)	Conus medullaris	Cauda equina (below the conus medullaris)
Evolution	Variable	Hyperacute	Subacute
Motor	Upper motor neuron	Upper and lower motor neuron disorder	Lower motor neuron
Sensory	Segmental with sacral sparing	Saddle	Dermatomal
Deep tendon reflexes	Increased	Increased or decreased depending on caudal extension of the lesion	Decreased
Incontinence	Late	Early	Late

Adapted from: Chamberlain MC. (2015) Neoplastic myelopathies. *Continuum (Minneapolis)*. 21: 132–145

### 43.5 Diagnosis

A recent study indicates that 62% of patients are ambulatory at the time of diagnosis [21, 22]. The mean time between the onset of symptoms and the definitive diagnosis is 3 months [18]. Neurologic examination must be the first step performed in this patient.

The presentation of a new symptom of back pain and/or neurological disorder in a cancer patient or in case of atypical pain in a non-oncological patient requires a more complex investigation, with more elaborate imaging exams than X-ray films [4].

Magnetic resonance imaging (MRI) is the most sensitive and the preferred method for early detection of NESCC [4, 7, 23, 24]. MRI provides a clear relationship between soft tissue and bone tissue, yielding accurate anatomic detail of bony compression or invasion of neural and paraspinal structures [24]. Therefore, accurately identifies and guides the physician about the exact location of the treatment performed on the patient, and furthermore, metastases can be distinguished from other pathologic processes (bacterial abscess, leptomeningeal carcinomatosis, intradural extramedullary tumors, inflammatory myelitis) [4, 25].

In patient who need a choice to MRI, one option is computed tomographic myelography. Computed tomography (CT) evaluates of the bone anatomy and the extent of the lesion within the bone. In this scenario, the benefit is greater if it is used

in conjunction with myelography in order to accurately determine the cord involvement, and being able to distinguish if caused by pathological fracture or tumor expansion [4, 7].

Bone scintigraphy is insufficient to assess the level of cord involvement. PET-CT cannot substitute for more detailed anatomic imaging techniques [4].

### 43.6 Treatment Guidelines

The primary goal of treatment is pain management and functional improvement. The expected practical outcome after therapy is largely dependent on pretreatment neurologic status. The three traditional mainstays of therapy have been corticosteroids, radiation therapy, and surgery.

Corticosteroids are the initial treatment in patients with suspected spinal cord compression, not only facilitate pain management but also reduce vasogenic cord edema and may prevent additional damage to the spinal cord from decreased perfusion. However, opioids are also usually required.

This treatment may require high doses of corticosteroids (dexamethasone – 4 mg every 6 h), which can lead to undesirable side effects [4, 26]. The intravenous application is made available to those who can not swallow. There are protocols with higher doses in the initial days of the symptoms (bolus of 100 mg followed by 96 mg divided into four doses for 3 days), but it remains unclear if their use leads to an improvement in neurologic recovery or preservation of motor function [27, 28].

The treatment options for patients with stable spinal disease include decompressive surgery, radiotherapy (RT), or both. In cases of instability of the spine, radiotherapy will not resolve the complication, and must be treated surgically with fixation or with percutaneous vertebroplasty (if there is no epidural disease) followed by RT. However, it is necessary to evaluate the stability of the spine using the SINS score (Fig. 43.2) [29]. Should be interpreted and conducted as follows: Score 13–18, spine unstable, patients should be nursed horizontally in bed, and a surgical approach considered; score 7–12, an indeterminate classification, possible impending instability, warrants surgical consultation; and score 0–6, stable spine.

The role of chemotherapy in this context should be used in very chemosensitive tumours and with presenting with stability of the spine. Solitary metastasis with indolent disease, may be candidates for attempted cure with en bloc resection (total spondylectomy) [30]. Radiotherapy alone if the tumour is very radiosensitive. But in most cases of stable spinal cord compression, the combination of decompression surgery followed by radiotherapy is preferable. Results in maintained ambulation in 94% treated with surgery and RT versus 74% for RT alone are observed in these patients [31].

The radiotherapy protocols consist of 5–10 applications of 3–4 Gy (total dose 30 Gy). There are some places that choose to perform higher daily doses (5 Gy) during a 3 days induction phase followed by daily fractions of 3 Gy over 5 days for consolidation [32]. Better local control and similar functional outcome, was



SINS Component	Score
<b>Location</b>	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
<b>Pain*</b>	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
<b>Bone lesion</b>	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
<b>Radiographic spinal alignment</b>	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
<b>Vertebral body collapse</b>	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
<b>Posterolateral involvement of spinal elements†</b>	
Bilateral	3
Unilateral	1
None of the above	0

**Fig. 43.2** Classification system for spinal instability in neoplasia disease. SINS, spinal instability neoplastic score. \*Pain improvement with recumbency and/or pain with movement/loading of spine. †Facet, pedicle, or costovertebral joint fracture or replacement with tumor. Adapted from: Fourny DR, Frangou EM, Ryken TC et al. Spinal Instability Neoplastic Score: an analysis of reliability and validity from the spine oncology study group. *Journal of Clinical Oncology* 2011; 29(22): 3072)

observed in long-course RT and it is generally reserved for those patients with better life expectancy.

Stereotactic radiosurgical may be an option for conventional RT, provides a higher radiation dose without exceeding the tolerance of the spinal cord, and is a good alternative for those who have progressed after RT or as adjuvant therapy after surgery [4].

The spinal cord decompression surgery is still a reason for intense discussions and deserves a more careful analysis. In selected patients, tumor resection has a greater functional benefit than irradiation (onset of neurological symptoms <48 h, younger patients, less radiosensitive tumors, no recent history of cancer, presence of pathological fracture causing compression, spine instability). Surgical morbidity is

considerable. This procedure includes resection of the affected vertebral body and implantation of stabilizing instrumentation [33].

It should be discussed on a case-by-case basis on the use of bisphosphonate in this scenario, since it can reduce skeletal-related events [34, 35].

### Questions

**1. The most common presenting symptom of spinal cord compression from tumor is:**

- (a) Paresthesias.
- (b) Pain.
- (c) Bladder retention.
- (d) Weakness.

**1. (b) Pain is the most common, early and consistent symptom in patients with metastatic spine disease.**

**2. The most effective surgical technique for spinal metastatic pathological fracture (in the correct clinical context) with spinal cord compression is:**

- (a) Laminectomy.
- (b) Laminectomy and instrumented fusion.
- (c) Posterior and anterior decompression and stabilization.
- (d) Cement augmentation.

**2. (c) When feasible, ventral and dorsal decompression with stabilization is ideal for the treatment of symptomatic pathological fractures, especially if kyphosis exists.**

**3. Man, 57 years old, presented with severe back pain and bilateral leg weakness for 3 days. Magnetic resonance imaging (MRI) of the spine reveals metastatic lesion in the vertebral body of T10 with significant spinal cord compression. What are the most likely primary tumors?**

- (a) Lung cancer and breast cancer
- (b) Lung cancer and lymphoma
- (c) Breast cancer and lymphoma
- (d) Colon cancer and prostate cancer

**3. (b) Although most patients with malignant medullary compression have a history of malignancy, about 20% develop this complication in the initial presentation. Breast cancer is the most common cause of this complication, but rarely occurs as an initial manifestation. The most common causes of malignant medullary compression in the presentation are lung cancer, non-hodgkin lymphoma, and multiple myeloma.**

**4. This patient was diagnosed with non-small cell lung cancer, what should be the initial measure taken for pain control?**

- (a) Chemotherapy
- (b) Corticosteroids

- (c) Anti-inflammatory
  - (d) Opioids
4. (b) Corticosteroids act not only to control the pain, but also reduce vasogenic cord edema and may prevent further damage to the cord.
5. **A woman on follow-up for breast cancer, a hormonal receptor positive, using aromatase inhibitor 3 years ago, starts atypical back pain in the thoracic spine without improvement with common analgesics. What is the best exam to apply for in this context?**
- (a) Request column RX
  - (b) Request Bone Cintology
  - (c) Request Computed Tomography
  - (d) Request column MRI
5. (d) Although the other tests have a good sensitivity to investigate bone metastases, the ideal is to request MRI in this context due to a better evaluation of the spinal cord, is the most sensitive and the preferred method for early detection of compression cord medullary.
6. It is known that in the treatment of ESCC the use of corticosteroid is intensively used. It is a complication of prolonged use of corticosteroids:
- (a) Cardiomyopathy
  - (b) Polyneuropathy
  - (c) Gastric ulcer bleeding
  - (d) Renal failure
6. (c) Gastric intolerance is a frequent symptom of the use of corticosteroids, even for those who take short periods of treatment. Patients in use concomitant use of drugs such as non-hormonal anti-inflammatory drugs and anticoagulants, are at increased risk of bleeding digestive, as well as the presence of neoplasia malignant, elderly and previous history of digestive ulcer, being in these cases indicated use of prophylactic drugs.
7. **Patient, 50 years old, with metastatic prostate cancer to the lumbar spine, initiates frame of weakness of lower limbs and symptoms of shocks during sneezing and coughs. Look for medical assistance, which is the best option below the next steps:**
- (a) Thorough evaluation of the lumbar spine and immediate treatment with neurosurgery if the spinal cord compression is confirmed.
  - (b) Thorough evaluation of the lumbar spine and immediate treatment with local radiotherapy if the spinal cord compression is confirmed.
  - (c) Thorough evaluation of the lumbar spine, and outpatient treatment with physiotherapy and corticosteroids if the spinal cord compression is confirmed.
  - (d) Thorough evaluation of the lumbar spine, and treatment with opioids and local radiotherapy if the compression of the spinal cord is confirmed.

7. (a) The approach with neurosurgery in this scenario is preferable since it is a young patient with a long life expectancy and the response to local radiotherapy does not overcome local surgical treatment aiming at quality of life.
8. **About malignant spinal cord compression is correct to affirm:**
- (a) The evaluation of the medullary stability is performed only by physical examination and patient complaints, with no need for complementary exam.
  - (b) It is important to evaluate the stable spinal disease according to the SINS score.
  - (c) The use of bisphosphonate is essential in the control of pain and follow-up of these patients.
  - (d) The best treatment for spinal instability is immediate radiotherapy.
8. (b) There is a score for spinal instability neoplastic score (SINS), which should be used for therapeutic decision. Score 13–18, spine unstable, score 7–12, an indeterminate classification, score 0–6, stable spine. In addition to the clinical evaluation, it is necessary to perform spinal imaging tests for this score.
9. **The resection en bloc is the treatment of choice for which of the following tumors in the spine?**
- (a) Lung metastasis
  - (b) Prostate metastasis
  - (c) Lymphoma
  - (d) Sacral chordomas
9. (d) Block resection is advocated for some solitary metastatic lesions in the spine. In this case wide en bloc spondylectomy is the treatment of choice for cases of chordoma or chondrosarcomas.
10. **What is the most frequent location of Epidural Spinal Cord Compression (ESCC)?**
- (a) Sacral spine
  - (b) Cervical spine
  - (c) Thoracic spine
  - (d) Lumbar spine
10. (c) Cervical spine is responsible for 15% of the ESCC presentation, 68% occurs in the thoracic spine and 16% in the lumbar spine. The over-representation of the thoracic involvement reflects the large thoracic spine size, as well as the comparatively small diameter of the thoracic spinal canal.
11. **Is it an option for the surgical treatment of spinal cord decompression when this is not possible?**
- (a) Local radiotherapy at the dose of 30Gy.
  - (b) Stereotactic radiosurgical.

- (c) High doses of corticosteroids
  - (d) A and B are correct.
11. (d) When surgery is not an option for the patient, radiotherapy should be the treatment of choice, and the stereotactic radiosurgical may be an option for conventional RT, provides a higher radiation dose without exceeding the tolerance of the spinal cord, and is a good alternative for those who have progressed after RT or as adjuvant therapy after surgery.
12. **Possible differential diagnoses to malignant medullary compression:**
- (a) Leptomeningeal carcinomatosis
  - (b) Inflammatory myelitis
  - (c) Bacterial abscess
  - (d) All are correct
12. (d) There are many benign causes of back pain and they should be excluded from possible malignancies, metastases can be distinguished from other pathologic processes (bacterial abscess, leptomeningeal carcinomatosis, intradural extramedullary tumors, inflammatory myelitis).
13. **It is not related to the pathophysiology of spinal cord compression:**
- (a) Axonal and white cord edema of the medullary cord is observed in at the onset of symptoms.
  - (b) Presence of the Batson epidural venous plexus in the spine.
  - (c) RANKL is deleted in bone metastases, whereas osteoprotegerin serum levels are overexpressed in patients with metastases bone.
  - (d) Hemorrhages and necrosis of white matter are observed at the later stage.
13. (c) RANKL (the main stimulator of bone resorption and formation / activation of osteoclasts) is overexpressed in bone metastases, whereas osteoprotegerin (OPG) serum levels (negatively regulate bone resorption by inhibition of osteoclasts) are decreased in patients with metastases bone.
14. **On the use of corticosteroids in the treatment of malignant medullary compression, which is the most used dosage of this medication:**
- (a) Dexamethasone – 4 mg every 12 h.
  - (b) Dexamethasone – 4 mg every 6 h.
  - (c) Dexamethasone bolus of 100 mg followed by 96 mg divided into four doses for 3 days.
  - (d) Dexamethasone – 8 mg every 6 h.
14. (b) This treatment may require high doses of corticosteroids (dexamethasone – 4 mg every 6 h), which can lead to undesirable side effects. There are protocols with higher doses but it is not yet clear whether there is a greater functional benefit in its use.

**15. What are the clinical criteria for the best benefit to indicate the surgical treatment of spinal decompression?**

- (a) Pathological fracture.
- (b) Poorly radiosensitive tumors (ex: melanoma).
- (c) Paresthesia of limbs in less than 48 h.
- (d) A, B and C are correct.

**15. (d)** In selected patients, tumor resection has a greater functional benefit than irradiation (onset of neurological symptoms <48 h, younger patients, less radiosensitive tumors, no recent history of cancer, presence of pathological fracture causing compression, spine instability).

**Clinical Case**

A 28-year-old man, with no pathological history, with clinical neoplasm of the testis. He reported the presence of a nodule in the left testicle, 5 months of evolution, not associated with trauma or fever. Three weeks later, he presented lumbar pain, type of slings, of moderate intensity and not disabling, without irradiation. With no other complaints, including motor or sensory changes.

On clinical examination, ECOG 0. On inspection of the genital tract was scrotal dysmorphism by enlargement of the left scrotal sac, 8 cm in diameter of stone consistency. He did not present palpable adenomegalias or alterations to the neurological examination. In USG scrotal it confirmed the presence of a solid, heterogeneous mass in the left testicle. Serum values of the tumor markers were AFP (4500 ng/ml),  $\beta$ -HCG (310 mUI/ml) and DHL (2030 U/L). Held a computed tomography (CT) thoraco-abdominal-pelvic for staging showed that pulmonary nodular lesions bilateral, abdominal, inguinal and mediastinal adenopathies.

He underwent left radical orchidectomy. The anatomopathological examination confirmed the presence of a germ cell tumor of non-seminomatous mixed pattern.

Three days after surgery was admitted for paresthesia of lower limbs, associated with low back pain with bilateral limb irradiation and abdominal wall, accompanied by urinary retention – less than 24 h of evolution. An MRI of the spinal axis showed changes in signal strength in the vertebral body of T12, of almost normal morphology, and a soft tissue component with space extension antero-lateral epidural, of L2-L4, corresponding to a possible compression of the spinal cord.

Corticosteroid therapy, analgesia and bladder catheter were started. Chemotherapy (QT) was urgently instituted, BEP scheme every 21 days, of which it fulfilled 4 cycles. There was progressive neurological improvement with resumption of ambulation after 2 cycles of chemotherapy and functional recovery of the urethral sphincter to the third cycle. MRI of the vertebral axis, 1 month after the onset of QT, demonstrated the disappearance of soft tissue mass within the medullary canal.

It continued performing motor rehabilitation, with progressive improvement of its functionality. Follows oncological follow-up and at the moment with negative markers.

## Comments

The present case report describes a clinical situation with medullary compression, which requires of an emerging intervention. MRI of the vertebral axis (sensitivity 0.44–0.93, specificity 0.90–0.98) constitutes the best examination to clarify the level and cause of the syndrome, according to published systematic reviews (Penas-Prado M et al).

Symptomatic treatment is of great importance for the control of pain, physical rehabilitation and prevention of interurrences. The etiologic treatment associates the accomplishment of corticoterapia, the chemotherapy, radiotherapy and/or surgery.

In this case, due to tumor chemosensitivity and in the absence of instability the early onset of chemotherapy was essential. Its efficacy in the treatment of spinal cord compression in patients with germ cell tumors has been described in series of cases since 1977; the largest series available (study retrospective; 1984–2009) included 29 patients with compression medullary (Grommes C et al., Cancer, 2011).

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# Chapter 44

## Superior Vena Cava Syndrome



**Maria Tolia, Nikolaos Tsoukalas, Ioannis Zerdes, Jiannis Hajjiannou, and George Kyrgias**

**Abstract** The superior vena cava syndrome (SVCS) involves a group of symptoms deriving from obstruction or compression of the [superior vena cava](#). Malignant causes represents the majority of all cases of SVCS. Iatrogenic causes may be responsible for SVCS, considering the presence of intravascular devices. Infectious causes such as [syphilis](#) and [tuberculosis](#) have also been known to cause SVCS.

Concerning the clinical presentation of SVCS may be subacute or acute. The most typical presenting symptoms and signs are dyspnea, facial edema, jugular venous distention, upper body plethora, cough, orthopnea, [stridor](#), chest pain, cyanosis, positive Pemberton's sign, dysphagia, visual impairment, lethargy, and headache.

Diagnosis is obtained by the aid of chest X-ray, CT and MRI scans, venography, and nuclear flow studies. In addition to these, invasive methods, such as bronchoscopy, percutaneous needle biopsy, mediastinoscopy, and thoracotomy, can also be applied.

Several methods of treatment are available. Endovascular stenting by an interventional radiologist may provide potential relief of symptoms, in an acute setting with severe symptoms. In the case of SVCS deriving from non-small cell lung cancer and other metastatic solid tumors, radiotherapy is the main treatment. Chemotherapy is effective in small cell carcinoma of the lung, lymphoma, and germ cell tumor. Surgery is helpful for patients in whom a benign process is the cause.

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Glucocorticoids have an ambiguous effect, as they may be useful at lymphomas but with no benefit on lung cancer. Diuretics with a low-salt diet and head elevation may also be beneficial.

**Keywords** Superior vena cava · Syndrome · Review

## 44.1 Introduction

The superior vena cava syndrome (SVCS) is an oncologic mechanical emergency that may dramatically affect patient distress [1].

It involves a range of symptoms and clinical signs deriving from intrinsic obstruction or external compression of the superior vena cava (SVC) or veins emptying into the SVC or the superior cavo-atrial junction [2]. SVCS leads to a serious reduction in venous return from the head, neck, and upper extremities. If there is a coexisting tracheal compression, superior mediastinal syndrome may be generated.

The transportation of blood from the head and neck, upper extremities and parts of the chest toward the superior-posterior right atrium of the heart is directed by the SVC, which is formed by the union of right and left brachiocephalic veins. This carries approximately a third of the entire venous return to the heart.

SVC is thin walled and it is located in a non-distensible area in the mediastinum. It can be easily influenced by extrinsic compression of primary tumors or lymph nodes in the middle or anterior mediastinum. Acute SVC obstruction may reduce cardiac output, yet after a period of a few hours a new steady state of blood return is accomplished through an increased venous pressure and collaterals to the azygos vein or the inferior vena cava [2]. Hemodynamic compromise is commonly caused by a great impact on the heart and not the SVC compression [3].

## 44.2 Epidemiology – Etiology

### 44.2.1 Infectious Diseases

Infectious diseases have been the main cause of SVCS for many centuries [2]. SVCS may be a result of an aortic aneurysm due to tertiary syphilis. An infectious mediastinitis deriving from granulomatous mediastinal diseases such as sarcoidosis and, more commonly, tuberculosis may generate a SVCS.

### 44.2.2 *Benign Causes*

An important factor of SVCS in benign cases is the application of intravascular devices (e.g. implantable defibrillators leads, pacemakers, permanent central venous access catheters, and port-a-caths) [4, 5]. Superior Vena Cava Syndrome with Cardiac Device-related Infective Endocarditis Secondary to Pacemaker Infection is also reported in literature [6, 7].

A previous infection with *Histoplasmosis*, actinomycosis, aspergillosis, blastomycosis, filariasis, rheumatic fever and nocardiosis can lead to fibrosing mediastinitis. This condition can be also met in patients having received prior thoracic external beam radiation therapy as a consequence of the local vascular fibrosis. SVCS may be a result of anthracotic calcified mediastinal lymphadenopathy accompanying recalcitrant pleural effusion [8].

Some additional factors are benign tumors, thyromegaly or Behcet's disease which is a vasculitis associating the affection of the SVC with venous thrombosis [9].

### 44.2.3 *Malignant Causes*

Intrathoracic malignancies have constituted approximately 90% of all SVCS cases for a period of about 25 years [2]. SVCS of malignant origin most commonly derive from non-small-cell lung cancer (50%), with small-cell lung cancer being the second cause (25%) and non-Hodgkin lymphoma the third (10%) [2]. Pediatric patients are more intensely imposed to this risk because of the fairly thin wall of the superior vena cava associated with the small intraluminal diameter of their vessels. This area is affected by external compression due to the amount of lymph nodes adjacent to the vena cava and the thymus that is quite prominent in the pediatric patients [10]. In another age group, the young adults, some of the most prominent causes of SVCS are malignant lymphoma and primary mediastinal germ cell tumor [11]. In the older patients age group, around 95% of all malignant SVCS cases derives from lung cancer and non-Hodgkin lymphoma (NHL) [4]. Two subtypes of NHL are generally connected with SVCS, the lymphoblastic lymphomas and the diffuse large B-cell lymphoma with sclerosis [12, 13].

Due to the fact that squamous and small cell histologies are most commonly localized centrally, they comprise about 85% of all malignant cases in lung cancer [11]. Other SVCS causes can be: Metastatic cancers to the mediastinum, such as testicular and breast carcinomas, Hodgkin's lymphoma, primary mediastinal tumors mesothelioma, teratoma and acute leukemias [2].

## 44.3 Diagnosis and Staging

### 44.3.1 Clinical Evaluation

The combination of various signs and symptoms is used for the diagnosis of SVCS. It is advisable that a thorough medical history with emphasis on malignant diseases and eventually recent intravascular procedures should be taken. In order that the patient's risk of adverse outcome is estimated, a physical examination with evaluation of central nervous and respiratory function is essential. A positive Pemberton's sign indicates SVCS. The maneuver is achieved by having the patient elevate both arms until they touch the sides of the face. The presence of facial congestion and cyanosis along with a respiratory distress after about 1 min indicates a positive Pemberton's sign.

The severity of symptoms is important in determining the urgency of intervention. Thus, a grading system is applicable in distinguishing between severe, life-threatening and nonlife threatening conditions. The severe symptoms group includes mild or moderate cerebral edema leading to headache and dizziness, mild or moderate laryngeal edema or cardiac reserve presented as syncope after bending. The life threatening group of symptoms involves notable cerebral edema generating confusion and obtundation, severe laryngeal edema leading to stridor and possible airway compromise, important hemodynamic compromise causing hypotension, syncope with no precipitating factors, and renal insufficiency [14]. A classification scheme of Lonardi et al. can be useful in categorizing the grading, the symptom severity and the intervention urgency [15]. The necessity of percutaneous stenting can be determined by the Kishi scaled scoring system [16].

### 44.3.2 Imaging – Staging

A chest radiograph can be applied for a SVCS diagnosis. The most critical finding concerns the widening of the right side of the superior mediastinum. What may also arise is pleural exudative effusion on the right side. In order to rule out the existence of a venous thrombus, doppler ultrasound can be used [17]. The chest computed tomography (CT) with intravenous contrast in the venous phase may be of great assistance for the diagnosis of information such as the tumor mass size, its localization, the SVC diameter and the length of the SVC stenosis. CT can also be useful for the planning of endovascular treatment. Superior vena cavography, performed prior to stenting, can aid in detecting thrombotic obstruction and thrombus extent in the SVC [18].

Two further diagnostic techniques that can be applied are magnetic resonance imaging (MRI) with MRI phlebocavography and phlebocavography with intrave-

nous contrast injection. Angiography with synchronous venous pressure gradient measurements and stenting can be carried out. For patients with no known history of malignancy invasive methods, including bronchoscopy, percutaneous needle biopsy, mediastinoscopy, and thoracotomy, can be applied. Biopsies with histological and/or cytological examination can rule out benign causes and reach a specific diagnosis to direct the most appropriate treatment. Bronchoscopy's features include the detection of an endoluminal tumor growth, the infiltration of central and peripheral ways and the obtainment of neoplastic tissue or cytological samples by the aid of brush, bronchial washing or bronchoalveolar lavage. Another less invasive diagnostic method may be offered for the biopsy of mediastinal lymph nodes [19, 20] through endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) and real-time convex-probe endobronchial ultrasound (CP-EBUS)-guided transbronchial needle aspiration (TBNA).

The introduction of more innovative mediastinoscopy techniques like video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA) offer both an optimal visualization and a more extensive sampling of mediastinal nodes with the surrounding fatty tissue, and can be used along with minimally invasive video-assisted lobectomy [21, 22]. Nodal status and mediastinal involvement may be further clarified with the use of positron emission tomography.

#### 44.4 Clinical Manifestation

Cervical hydrostatic venous pressure normally fluctuates between 2 and 8 mm Hg, and with the SVC obstruction it can reach up to ten-fold (20–40 mm Hg) [2]. This may lead to a distension of subcutaneous vessels of the anterior chest wall, providing collateral circulation. The principal collateral pathways are: (a) azygos/hemiazygos – intercostal veins, (b) internal mammary – their tributaries veins, (c) conjunctions to the superior – inferior epigastric veins, (d) long thoracic – femoral/vertebral veins. If the obstruction is located above the azygos, then the clinical picture can be milder with a potential of improvement when collateral circulation develops.

Some of the most common patients' symptoms include visibly dilated neck veins, facial plethora (of the eyelids in particular) and edema of the neck, chest and arms. Edema of the larynx or pharynx that results in hoarseness, cough, stridor, dyspnea, orthopnea, cyanosis, glossal swelling and dysphagia can be present in more severe cases. SVC obstruction impairs venous return to the right atrium, which may lead to complications, such as cerebral edema with neurologic alteration may be subtle, causing headaches, papilledema, dizziness, syncope, hypotension, lethargy, confusion, and eventually coma. Cerebral and/or laryngeal edema signs and symptoms must be urgently evaluated.

A mediastinal mass can cause direct heart compression associated with hemodynamic alterations and cardiorespiratory symptoms at rest. As a consequence cardiac arrest or respiratory failure can occur. One of the late complications of chronic SVCS can be esophageal varices with bleeding.

## 44.5 Treatment Approaches

Symptoms alleviation may be achieved through some maneuvers (e.g. head elevation) as they can reduce hydrostatic pressure in the upper half of the body [23]. In case of dyspnea supplemental oxygen is recommended. What should be avoided, however, is the use of intramuscular and intravenous injections in the upper extremities, as, in combination with the slow venous return, the delayed drugs absorption from the surrounding tissues may result in thrombosis of veins and irritation. Glucocorticoids are recommended in patients with steroid-sensitive tumors including lymphoma or thymoma, and for patients who want to avoid swelling due to radiotherapy (RT).

Life-threatening cases may demand for empiric therapies with stenting and radiation prior to the pathological results. Steroids might be justified for patients with preexisting laryngeal edema [24]. Diuretics, fluid restriction and a low-salt-diet should also be taken into consideration [25]. In case of SVCS from an intravascular thrombus associated with an indwelling catheter, catheter removal and systemic anticoagulation should be combined in order to prevent embolization [2]. However, the catheter can be kept in case of an early detection of the SVCS and an application of a fibrinolytic therapy [26]. Infectious etiologies can be managed with antibiotics.

Management of the SVCS relies on histology type, staging of the disease, previous therapies and prognosis. Treatment methods involve SVC stenting, irradiation, chemotherapy, and bypass surgery. Tracheal obstruction, cardiac compression and hypotension or syncope without preceding factors, comprise possibly life-threatening complications of a SVCS. Grade 3, 4 or 5 symptoms demand urgent endovascular interventions, including angioplasty, stenting, and pharmacomechanical thrombolysis, or surgery [27].

## 44.6 Locoregional Therapy

### 44.6.1 Endovascular Stenting

An emergent therapy is needed in case of an upper airway obstruction and must be immediately alleviated with the aid of intravascular self-expanding stents with anticoagulation. In presence of severe symptoms, early stenting may be necessary. SVC

stenting is a viable palliative option and improves quality of life. SVCS patients may be recurrence-free prior to exitus from the underlying neoplasm [28, 29]. Although unilateral stent placement may prove to be efficient, certain cases demand for bilateral stent placement in both brachiocephalic veins and the SVC.

### 44.6.2 Radiotherapy

Before the era of endovascular stenting, RT was the sole treatment recommended to all SVCS patients. Modern therapeutic approach, the treatment involves prompt stent placement, then a tissue biopsy and finally, RT and/or chemotherapy [30, 31].

Even though it can improve symptoms, there are histological subtypes that can be radioresistant and there have been reported irradiation response times of more than 30 days [31–33].

For epithelial tumors, concurrent chemoradiation seems superior rather than sequential chemotherapy followed by RT [2]. Concomitant chemoradiotherapy, seems more effective in comparison with sequential chemoradiotherapy since it can offer a better locoregional control [34]. The addition of induction chemotherapy to concurrent chemoradiotherapy adds toxicity and provides no benefit for local-regional tumor control over concurrent chemoradiotherapy even for certain non-Hodgkin lymphoma subtypes [2, 35].

Following SVC stenting, the most recommended treatment is concurrent radiation therapy along with chemotherapy so as to increase the clinical benefit and minimize the possibilities of a tumor growth in the stent (tertiary prevention). There is limited data in randomized trials comparing RT fractionation schemes and in retrospective evidence [36]. Poor performance status patients may be greatly relieved from suffering and experience a quality of life improvement through hypofractionated RT (large dose per fraction, less fractions) [37]. The more effective schemes involve delivery of higher doses of 3–4 Gy for the first 2–5 fractions followed by a 2 Gy fractionation, to a total dose of approximately 30–50 Gy [36]. Selected patients (limited stage Small Cell Lung Cancer-SCLC, stages II, III Non Small Cell Lung Cancer – NSCLC, low grade lymphoma), may receive a radical definitive RT scheme or a multi-modality treatment. What may be of consideration is the application of strategies initializing with RT with higher doses 3–4 Gy for the first 2–3 days and then a conventional fractionation of 1.8–2 Gy per day to deliver a total curative dose [38].

In some cases of inoperable early stage lung cancer related to SVCS, an advanced RT technique, the stereotactic body radiation therapy (SBRT) can be applied. SBRT's advantage lies in the fact that it can deliver high doses per fraction to alleviate SVCS symptoms while at the same time offering definitive treatment and high rates of local control [39]. Non radiosensitive tumors can be dealt with SBRT as an alternative RT technique.

## 44.7 Systemic Therapy

### 44.7.1 Chemotherapy – Immunotherapy

Chemotherapy seems to be a mainstay of treatment for the SVCS patients with SCLC, non-Hodgkin lymphoma and germ cell tumors, as these neoplasms are particularly chemo-sensitive [17, 40, 41].

The role of chemotherapy for SVCS in NSCLC remains uncertain [42].

The efficacy of SVCS treatment with tyrosine kinase inhibitors (TKIs) has limited data [43, 44].

Maki et al. [43] published a case of metastatic dermatofibrosarcoma protuberans with SVCS that had symptom relief from imatinib which functions as a specific inhibitor of a number of tyrosine kinase enzymes (TKI).

The combination of RT with cetuximab was studied in a phase II study in elderly and/or poor performance status patients with locally advanced non-small cell lung cancer.

The adverse event profile appeared acceptable and more than 50% of patients lived beyond 11-months. The combination of RT with cetuximab might be effective, since over-expression of epidermal growth factor receptor reduces radiosensitivity, and radiation therapy may up-regulate the epidermal growth factor receptor. This combination merits further study in SVCS patients [44].

## 44.8 Future Developments

A randomized controlled phase III trial comparing chemotherapy to irradiation based on the tumor histology.

The abscopal effect from the combination of Stereotactic Body Radiotherapy or hypofractionated RT and targeted agents needs further evaluation.

There are no randomized trials comparing RT fractionation schemes.

### Key Points

**Introduction:** SVCS represents an oncologic mechanical emergency. It is a group of symptoms and signs caused by intrinsic obstruction or external compression of the SVC or veins emptying into the SVC or the superior cavo-atrial junction.

### Epidemiology – Etiology

- A. Infectious Diseases: Syphilis, sarcoidosis, tuberculosis, histoplasmosis, actinomycosis, aspergillosis, blastomycosis, filariasis, rheumatic fever and nocardiosis.
- B. Benign Causes: intravascular devices, benign tumors, thyromegaly, Behçet's disease.



- C. **Malignant Causes:** NSCLC, SCLC, NHL, germ cell tumor. Metastatic cancers to the mediastinum: testicular, breast carcinomas, HL, mesothelioma, teratoma, acute leukemias.

### Diagnosis and Staging

**History and Physical examination.** Life threatening symptoms: cerebral edema causing confusion, laryngeal edema causing stridor and potential airway compromise, significant hemodynamic compromise causing hypotension, syncope without precipitating factors and renal insufficiency.

**Imaging:** The diagnosis of a SVCS can be made on a chest radiograph, doppler ultrasound, chest computed tomography, superior vena cavography, magnetic resonance imaging, angiography, bronchoscopy, percutaneous needle biopsy, mediastinoscopy, and thoracotomy, endobronchial ultrasound guided transbronchial needle aspiration, mediastinoscopy.

**Clinical Manifestation** Facial plethora, edema of the neck, chest and arms. More severe cases include edema of the larynx or pharynx that leads to hoarseness, cough, stridor, dyspnea, orthopnea, cyanosis, glossal swelling, dysphagia, cerebral edema headaches, papilledema, dizziness, syncope, hypotension, lethargy, confusion, and eventually coma.

**Treatment Approaches** In intravascular thrombus from indwelling catheter, catheter removal and systemic anticoagulation. Infectious etiologies can be managed with antibiotics.

Management of oncologic SVCS depends on histology type, staging of the disease, previous therapies and prognosis. Treatment modalities include SVC stenting, irradiation, chemotherapy, and bypass surgery.

### Multiple-Choice Questions

#### 1. What is the most common benign etiology of SVCS?

- (a) The use of intravascular devices
- (b) The aortic aneurysm due to tertiary syphilis
- (c) Granulomatous mediastinal sarcoidosis
- (d) Infectious tuberculosis mediastinitis
- (e) Fibrosing mediastinitis due to a prior infection with *Histoplasmosis*, actinomycosis, aspergillosis, blastomycosis, filariasis, rheumatic fever and nocardiosis.

#### 2. What is the most common malignant etiology of SVCS?

- (a) Small-cell lung cancer
- (b) Non-small-cell lung cancer
- (c) Non-Hodgkin lymphoma
- (d) Primary mediastinal germ cell tumor

3. **What is the most common metastatic cancer to the mediastinum that causes SVCS?**
  - (a) Testicular
  - (b) Breast carcinomas
  - (c) Hodgkin's lymphoma
  - (d) Mesothelioma
  - (e) Teratoma
  - (f) Acute leukemias
  - (g) All above
4. **What is the most life threatening SVCS symptoms?**
  - (a) Confusion and obtundation due to cerebral edema
  - (b) Stridor and potential airway due to laryngeal edema
  - (c) Hypotension due to significant hemodynamic compromise
  - (d) Syncope
  - (e) All above
5. **What is the positive sign indicative of SVCS?**
  - (a) Adson's sign
  - (b) [Hampton's hump](#)
  - (c) Pemberton's sign
  - (d) Peabody's sign
  - (e) Hippocratic fingers
6. **What is the most common diagnostic method based on which the diagnosis of a SVCS can be made?**
  - (a) Chest radiograph
  - (b) Chest computed tomogram (CT) with intravenous contrast
  - (c) Superior vena cavography
  - (d) Bronchoscopy
  - (e) Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA)
7. **What is the most important collateral pathway?**
  - (a) Azygos/hemiazygos – intercostal veins
  - (b) Internal mammary – their tributaries veins
  - (c) Conjunctions to the superior – inferior epigastric veins
  - (d) Long thoracic – femoral/vertebral veins
  - (e) All above
8. **What is the treatment of choice in grade 3–5 SVCS symptoms?**
  - (a) Urgent endovascular interventions
  - (b) Pharmacomechanical thrombolysis,
  - (c) Surgery

- (d) a + b
- (e) a + b + c

**9. What is the optimal radiotherapy regimen?**

- (a) Hypo-fractionated RT
- (b) Higher doses of 3–4 Gy for the first fractions followed by a 2 Gy fractionation
- (c) Not known

**10. In which tumor chemotherapy seems to be a mainstay of SVCS treatment?**

- (a) SCLC
- (b) Non-Hodgkin lymphoma
- (c) Germ cell tumors
- (d) a + b + c
- (e) NSCLC

**11. Which radiotherapy technique could be an alternative in non radiosensitive tumors?**

- (a) Three dimensional conformal radiotherapy (3D-CRT)
- (b) Intensity Modulated Radiotherapy (IMRT)
- (c) Stereotactic body radiation therapy (SBRT)
- (d) None

**12. Infectious SVCS etiologies can be managed with which of the following?**

- (a) Antibiotics
- (b) Irradiation
- (c) Chemotherapy
- (d) Cetuximab
- (e) Imatinib

**13. Which tyrosine kinase inhibitor (TKI) was evaluated in a patient of dermatofibrosarcoma protuberans with SVCS?**

- (a) Gefitinib
- (b) Imatinib
- (c) Erlotinib

**14. Why the combination of radiotherapy with cetuximab might be effective in SVCS?**

- (a) Over-expression of epidermal growth factor receptor reduces radiosensitivity
- (b) Radiation therapy may up-regulate the epidermal growth factor receptor
- (c) It was studied in a phase II study in elderly and/or poor performance status patients with locally advanced non-small cell lung cancer.
- (d) All above

**15. Which classification scheme can be used in order to determine the SVCS grading, the symptom severity and the urgency of intervention?**

- (a) Lonardi
- (b) Kishi
- (c) WHO toxicity grading scale for determining the severity of adverse events

**Answers**

**1a:** The use of intravascular devices (e.g. implantable defibrillators leads, pacemakers, permanent central venous access catheters, and port-a-caths).

**2b:** Non-small-cell lung cancer represents the most frequent cause of SVCS of malignant origin (50%)

**3 g:** All above

**4e:** All above

**5c:** Pemberton's sign: The maneuver is achieved by having the patient elevate both arms until they touch the sides of the face. A positive Pemberton's sign is marked by the presence of facial congestion and cyanosis, as well as respiratory distress after approximately 1 min.

**6a:** The diagnosis of a SVCS can be made on a chest radiograph.

**7e:** All above

**8e:** Grade 3, 4 or 5 symptoms require urgent endovascular interventions, including angioplasty, stenting, and pharmacomechanical thrombolysis, or surgery.

**9c:** There are no randomized trials comparing RT fractionation schemes

**10d:** Chemotherapy seems to be a mainstay of treatment for the patients with SCLC, non-Hodgkin lymphoma and germ cell tumors, as these neoplasms are particularly chemo-sensitive. The role of chemotherapy for SVCS in NSCLC remains uncertain.

**11c:** SBRT maybe an alternative RT technique in non radiosensitive tumors due to the delivery of higher doses per fraction.

**12a:** Infectious etiologies can be managed with antibiotics.

**13b:** A case of metastatic dermatofibrosarcoma protuberans with SVCS had symptom relief from imatinib.

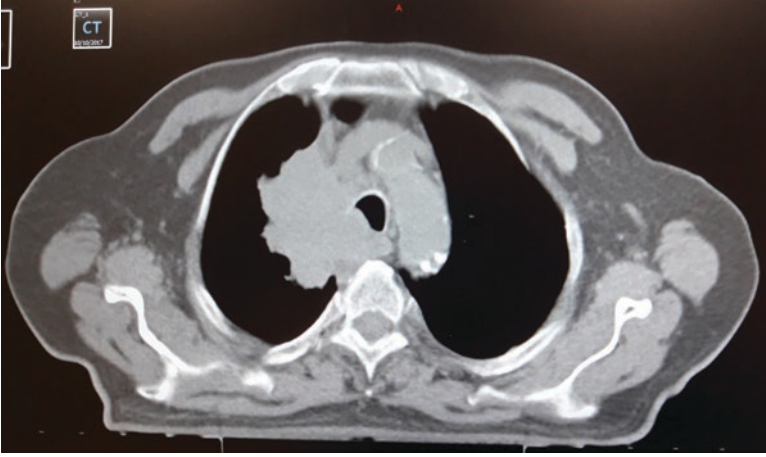
**14d:** The combination of RT with cetuximab was studied in a phase II study in elderly and/or poor performance status patients with locally advanced non-small cell lung cancer. The adverse event profile appeared acceptable and more than 50% of patients lived beyond 11-months. The combination may be effective, since over-expression of epidermal growth factor receptor reduces radiosensitivity and radiation therapy may up-regulate the epidermal growth factor receptor.

**15a:** The classification scheme of Lonardi can be used.

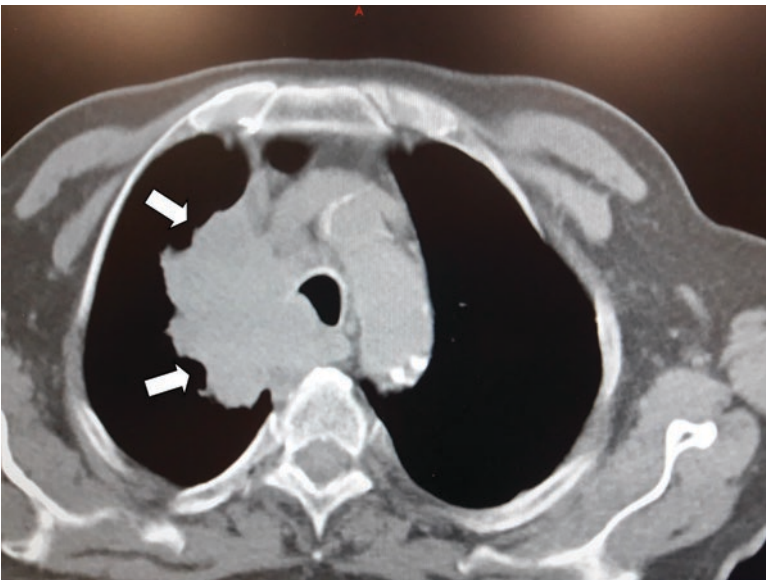
**Clinical Case**

A 49-year-old woman with a history of chest pain, dyspnea when supine and anorexia was referred to our hospital. She had no other relevant medical history known and she was not a smoker. She presented with sudden neck edema and facial plethora. She was immediately admitted to the hospital. Routine laboratory tests revealed mild normocytic anemia in CBC and a normal BMP. An hypoxemia was shown in arterial blood gas analysis. A CT revealed tumor involvement of the SVC

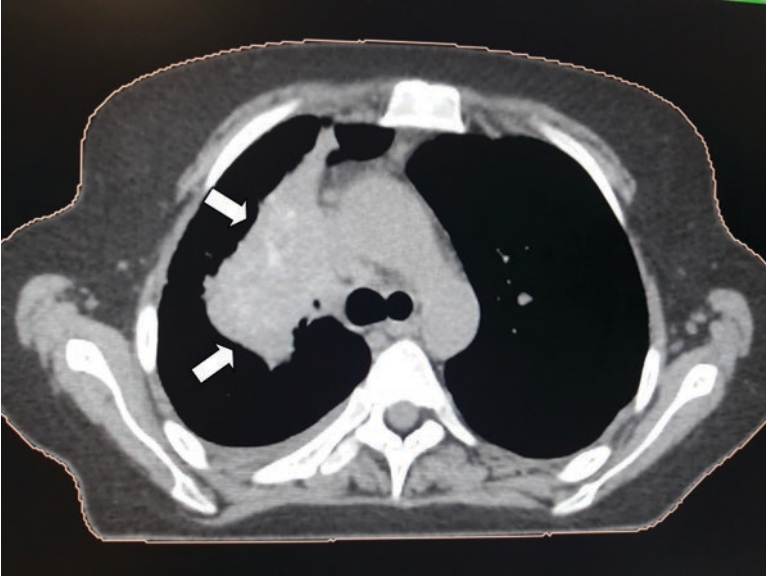
[See also Figs. 44.1, 44.2, and 44.3] without other distant metastatic sites. A diagnosis of adenocarcinoma was based on bronchoscopy and needle biopsy. A three-dimensional conformal radiotherapy with conventional fractionation of 2 Gy/fraction to deliver a curative total dose of 60 Gy was started [See also Figs. 44.4 and 44.5]. The patient had almost immediate resolution of clinical symptoms.



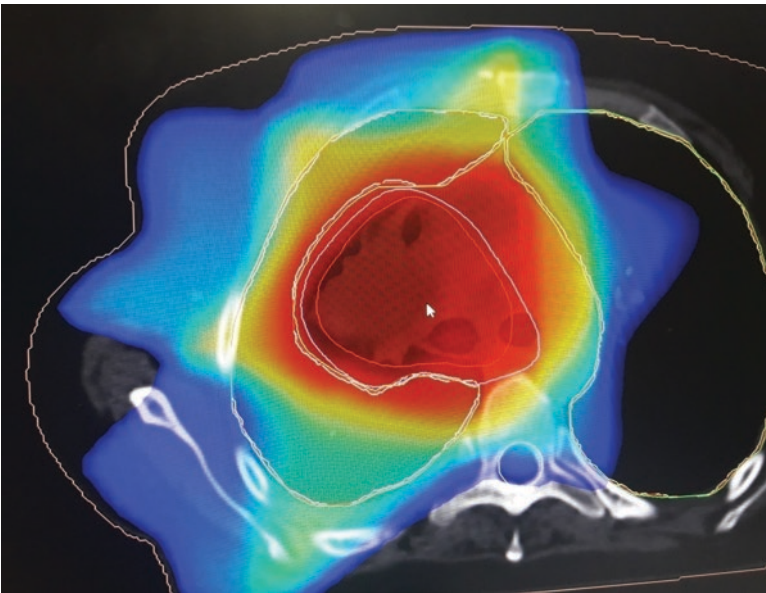
**Fig. 44.1** Axial contrast-enhanced computed tomography scans of upper chest shows compression of superior vena cava by tumor (white arrows)



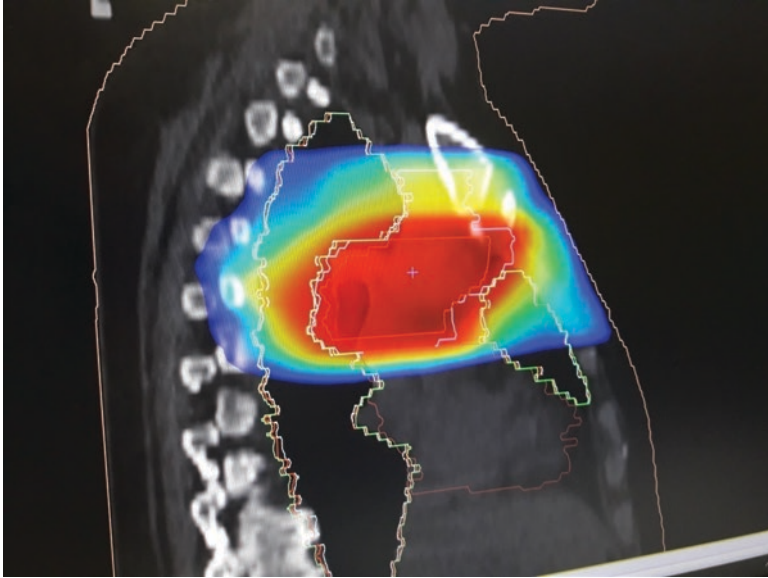
**Fig. 44.2** Axial contrast-enhanced computed tomography scans of upper chest shows compression of superior vena cava by tumor (white arrows)



**Fig. 44.3** Axial contrast-enhanced computed tomography scans of upper chest shows compression of superior vena cava by tumor (white arrows)



**Fig. 44.4** Radiation dose-distribution in an axial view. Colored contours represent the percentage of the total prescribed dose (Red: 100% of the total dose = 60 Gy)



**Fig. 44.5** Representative dose distribution in sagittal view (Red: 100% of the total dose = 60 Gy)

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# Chapter 45

## Current Treatment of Febrile Neutropenia



### Focused on the Individual Who Undergoes Treatment for Breast Cancer

Samantha Chao and Bora Lim

**Abstract** Chemotherapy-induced neutropenia (CIN) is a common side effect of anticancer drugs used for treatment of solid tumors. Neutropenic cancer patients are more than 50 times more likely to develop an infection, often bacterial, which can develop febrile neutropenia (FN), a toxicity that requires rigorous treatment. FN is not only potentially life-threatening, but may also alter the patient's chemotherapy schedule to impact their long-term outcomes. The significant impact of CIN and FN on cancer patients makes it imperative to develop a standardized guideline of prophylactic treatment of CIN. Thus, we conducted a literature review to provide a guideline that compiles guidelines from reputable cancer treatment institutions. Currently, guidelines differ slightly between sources and yet agree upon the vast majority of core practice to ensure the patient safety which we present here to provide as a practice guideline.

**Keywords** Neutropenic fever · Febrile neutropenia · Post-chemotherapy neutropenia

## 45.1 Introduction

Breast cancer accounts for a large amount of diagnoses, with an estimated 266,120 new cases diagnosed in women in the United States every year, and more so world wide [1]. Conversely, the mortality rate has gone down in the past years with the advent of stronger, more targeted anticancer drugs [2]. However, a common side

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effect associated with anticancer treatment is chemotherapy-induced neutropenia (CIN), with 37% of BC patients experiencing a decrease in the absolute neutrophil count (ANC) below 500 cells/mm<sup>3</sup> [3]. Cancer patients can be in danger of transient immunosuppressive status secondary to chemotherapy, and exposed to morbidity and mortality [4]. Cancer patients can have significant myelosuppression secondary to chemotherapy treatment, which increases susceptibility to infection as a result of disruption in the mucosal barrier in the gastrointestinal tract, in addition to translocation from other sites as well as indwelling foreign devices that may be colonized. Fever may often be the only sign of infection due to diminished ability to mount an inflammatory response. Since morbidity and mortality caused by neutropenic infection complications are so high [5], it is imperative that empirical antimicrobial treatment is promptly instituted when fever develops. Choice of antimicrobials is based primarily on degree and duration of neutropenia with broad spectrum agents used for patients with severe, profound and prolonged neutropenia who have a higher risk of adverse outcomes. While therapeutics to treat breast cancers may not induce as much as neutropenic fever as other diseases, e.g., hematologic malignancy or stem cell transplantation, still patients suffer from this complications [6]. Physicians must be aware of these guidelines, as well as infection risks, diagnostic methods, and antimicrobial therapies required for managing febrile patients through the neutropenic period. Thus, here we review current updated data and guidelines for neutropenic fever, focusing on patients who undergo breast cancer targeted treatments.

## 45.2 Definition of Neutropenic Fever/Febrile Neutropenia

Neutropenia is defined by the Common Terminology Criteria for Adverse Events (CTCAE) as “a finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen” [3]. The CTCAE has categorized neutropenia into four grades of severity based on the absolute neutrophil count (ANC):

- Grade 1: ANC from the lower normal limit to 1500 cells/mm<sup>3</sup>
- Grade 2: ANC from 1500 to 1000 cells/mm<sup>3</sup>
- Grade 3: ANC from 1000 to 500 cells/mm<sup>3</sup>
- Grade 4: ANC <500 cells/mm<sup>3</sup>

There are no universally agreed upon cut-off values for either temperature or ANC count for definition of FN internationally. For instance, the American Society of Clinical Oncology (ASCO) defines an absolute neutrophil count of less than 1000 cells per microliters as neutropenia, and refers to it as profound and severe if counts are below 500 and 100 cells per microliters respectively. Infectious Disease Society of America (IDSA) on the other hand uses a cutoff of less than 500 cells per microliters as a definition of neutropenia.

The longer the duration of neutropenia, the more likely patients are to develop febrile neutropenia. Febrile neutropenia (FN) is defined by the European Society for Medical Oncology (ESMO) as a temperature of greater than 38.5 °C or two consecu-

tive readings of greater than 38 °C for 2 h while the ANC is below 500 cells/mm<sup>3</sup> [7]. Patients with an ANC of less than 500 cells/mm<sup>3</sup> for greater than 7 days are likely to develop FN, thus needs to take caution/preventive measures not to be exposed to possible infectious source. To define the febrile status here, ASCO endorses a body temperature of greater than equal to 38.3 °C as fever in the setting of neutropenia. IDSA uses a higher cutoff of 38.5 °C but considers a temperature of 38.0 °C that persists for 2 h or more as fever as well [8].

Taking these guidelines for evaluation of neutropenic breast cancer patients into account, a sustained temperature of greater than 38 °C for over 1 h or one time reading of 38.3 °C is generally agreed upon as a definition of fever of neutropenia if the absolute count is less than 500 cells per microliters or is expected to drop below this level in the next 48 h, in which temperatures are measured using non-invasive methods such as infrared tympanic temperature measurements.

### 45.3 Risk Factors of Developing Neutropenia

A prompt assessment of possible source of infection should be undertaken at presentation of fever for patients who are at risk of FN. However, it is helpful if health care professional is aware of the degree of risk. Few clinical characteristics also contribute to the different risk of FN. Old age, poor performance status (PS), impaired nutritional status, female gender all are considered as risk factors. Previous history of myelotoxicity, extent of disease, hematologic malignancies are also considered as high-risk factors. Among breast cancer patients, the patients who are exposed to dose-dense anthracycline/taxan and docetaxel-based regimens are main ones who are at risk of developing FN but any patients who are exposed to myelosuppressive drugs carry >20% risk of developing neutropenia. In the analysis of Chinese patients who undergo anthracycline based chemotherapy for breast cancer treatment, the occurrence rate was higher among patients with low body mass index (BMI) (<23 kg/m<sup>2</sup>), with odds ratio (OR 4.4, 95% CI = 1.65–12.01, p = 0.003) [6].

### 45.4 Source of Infectious Organisms

Historically, gram-negative bacteria like *Pseudomonas* have been the cause of severe infection, mostly trans-locating across the breached mucosa of the gastrointestinal tract. However, lately, there has been a shift towards more gram-positive organisms. Increased and prolonged use of indwelling infusion catheters has been often be the source of infection. Fungal and viral infections are more common in patients with prolonged neutropenia and a history of multiple chemotherapeutic uses.

Currently, coagulase negative Staphylococci are the most frequently identified organisms from blood cultures but the incidence of multi drug resistant gram-negative organisms is on the rise as well. That said, often, the causative organism is

**Table 45.1** Common bacterial pathogens in febrile neutropenia patients

Common gram-positive pathogens			Common gram-negative pathogens		
Organisms	Resistance mechanism	Mode of entry	Organisms	Resistance mechanism	Mode of entry
<b>Coagulase-negative staphylococci</b>		CVC	<b>Escherichia coli</b>	Extended spectrum beta-lactamase	Bowel mucosa
<b>Staphylococcus Aureus</b>	Methicillin-resistant	Skin, CVC	<b>Klebsiella species</b>	Carbapenemase-producing	Bowel mucosa
<b>Enterococcus species</b>	Vancomycin resistance	Urine, CVC			

CVC central venous catheter

not identifiable from cultures in a patient with febrile neutropenia. Anaerobic and polymicrobial infections appear to be a less common source of infection in febrile neutropenia patients (Table 45.1).

Shift from gram-negative organisms and rise in incidence of gram-positive bacteremia is in part due to use of prophylactic antibiotics that predominantly have a gram-negative coverage and increased use of chronic indwelling venous catheters respectively. However, more severe infections are still caused by gram-negative organisms.

Fungal infections are a less common cause of initial fever in the setting of neutropenia. However, the risk of fungal infection increases with the duration and severity of neutropenia, prolonged use of antibiotics and number of chemotherapy cycles given [9]. *Candida* spp. and *Aspergillus* spp. are the most common causes of disseminated fungal infection. *Candida* often colonizes the gut and is translocated across a breached mucosa in neutropenic patients, whereas the mode of transmission of *Aspergillus* is inhalation. *Candida Albicans* account for most cases of candida infections, however, incidence of non *Albicans* *Candida* species is on the rise given frequent use of fluconazole in this patient population. Life threatening ‘rhino-orbital-cerebral’ infections by Mucormycosis is not uncommon in immunocompromised patients and therefore health care providers should have a low threshold for suspicion for this. In patients who live in or travel to endemic areas, reactivation of endemic fungi (*Histoplasma Capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides* spp.) should also be considered.

Viral infections, especially secondary to reactivation of human herpes viruses, are common in high-risk neutropenic patients. Most HSV 1 and HSV 2 infections occur because of reactivation in immunocompromised host and can cause of wide array of clinical manifestations, ranging from ulceration of oral/genital mucosa to meningitis, encephalitis and myelitis. Varicella Zoster Virus tends to cause disseminated infection as well in immunocompromised host. Primary infection and reactivation of CMV, EBV and HHV 6 are also seen in patients who have undergone hematopoietic stem cell transplant and can cause of wide range of problems including significant bone marrow suppression.

## 45.5 Prevention of Febrile Neutropenia

Prophylactic antibiotics such as myeloid growth factors exhibit some efficacy at reducing the risk of febrile episodes in neutropenic patients with BC. There is evidence that they reduce the risk of FN and infection in patients. Granulocyte colony-stimulating factor has demonstrated, through randomized controlled trials, a significant reduction in infection-related and early all-cause mortality as it improves delivery of chemotherapy dose intensity. For patients receiving chemotherapy associated with a 20% or greater risk of FN, current guidelines recommend primary prophylaxis with myeloid growth factor. Truong et al. analyzed total of 130 studies with various regimen to treat cancer including >50,000 patients. In this study, randomized study represented more accurate rate of FN, which was 13% [10].

Given the importance, reputable cancer organization publishes the guidelines for the use of growth factor, including short and long acting agents. In breast cancer, a multi-center, double-blinded, randomized phase III study was conducted using peg-filgrastim in patients who undergo treatment for breast cancer. This study published by Vogel et al., showed that a significant lower risk of FN (1% vs 17%, in prophylactic filgrastim using arm vs not, respectively), as well as FN related hospitalization (1% vs 14%), use of IV antibiotics (2% vs 10%), supporting the role of prophylactic use of neutrophil support as part of standard care for patients with breast cancer [11]. Indeed, some regimens in breast cancer treatment, e.g., dose dense AC or taxol, the use of supportive filtrastim or pegfilgrastim is mandatory.

## 45.6 Management of Neutropenic Fever

### 45.6.1 *History Taking and Physical Exam: Risk, Source Assessment*

Patient history and physical examination should be a primary factor when assessing a neutropenic patient for fever, with special attention paid to signs and symptoms that can help determine any sources of infection. Information about duration and severity of neutropenia and other co-morbidities can be used to identify patients as high-risk or low-risk, which affects the rigor of empirical treatment. Risk assessment can help determine the type of empirical antibiotic therapy (IV vs. oral), venue of treatment (inpatient vs. outpatient), and duration of antibiotic therapy. MASCC and CISNE risk stratification can be utilized [12].

High-risk patients exhibit or are anticipated to have prolonged (greater than 7 days) and profound neutropenia (ANC less than 100 cells/mm<sup>3</sup> following cytotoxic chemotherapy) with significant co-morbidities such as hypotension, pneumonia, new-onset abdominal pain, and neurological changes [4]. They may present in extremis, with signs of hypotension and respiratory distress. These individuals may only have significant fatigue as a presenting symptom. Steroids also tend to mask

fevers and should be taken into consideration when evaluating a patient with neutropenia.

Low-risk patients exhibit a brief duration (less than or equal to 7 days) of neutropenia with few to no co-morbidities. They are good candidates for oral empirical therapy and can be treated with outpatient empirical antibiotic therapy [4]. Formal risk classification can be performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system as an example. Many institutions carry their own guideline of assessing risk for patients who came in for the urgent care [13] (Table 45.2).

Patients with high scores are at higher risk while those who score higher are at lower risk. High-risk patients are defined by IDSA guidelines as having a MASCC score of less than 21. Low-risk patients are defined by IDSA guidelines as having a MASCC score of greater than or equal to 21 [4]. It is important to note that a subset of patients deemed low-risk by the MASCC scoring system may go on to develop serious complications. Among these are patients with a major abnormality or significant clinical worsening since the most recent chemotherapy or onset of neutropenia with respect to any of the following: organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, and/or documented anatomic site of infection.

#### 45.6.1.1 Laboratory Workup

After clinical evaluation, laboratory tests should be performed. Tests should include a complete blood cell (CBC) count with differential leukocyte count and platelet count; chemistry panel. At least two sets of blood cultures are recommended, with each set collected simultaneously from each lumen of an existing central venous catheter (CVC), or from two separate venipunctures if no central catheter is present. Culture specimens from other sites of suspected infection should be obtained as clinically indicated, and a chest radiograph should be ordered for patients with respiratory symptoms.

**Table 45.2** The multinational association for supportive care in cancer risk-index score (MASCC)

Characteristic	Characteristic Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure $\geq 90$ mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age $\geq 60$ years	2

MASCC risk-index score [13]

### 45.6.1.2 Antibacterial Antibiotics

High risk patients require hospitalizations for empirical broad spectrum intravenous antibiotic therapy, and necessary supportive care depends on the degree of severity. A low threshold of suspicion is crucial to identifying neutropenic patients who may not present with fever but go on to develop septicemia. Duration of antibiotic treatment is determined by the underlying condition, suspected route and source of infection. If no evidence of source of infection is found, treatment should at least be continued till the time of absolute neutrophil count recovery to greater than  $>500$  cells/mm<sup>3</sup>, provided patient has remained afebrile. A broad -spectrum antibiotic, with or without multiple drug resistant gram-positive coverage (determined by degree of suspicion of the central line infection or presence of hemodynamic compromise), should be instituted within an hour of presentation per ASCO recommendations [14].

Gram-positive organisms have been a predominant bacterial pathogen for febrile neutropenia. Monotherapy with a broad spectrum, anti-pseudomonal, beta lactam drug is recommended as the initial therapy. Drugs that fall under this category include cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam. Approximately 10%–15% of bacteremias are polymicrobial, which encourages the use of combination regimens. Vancomycin is not recommended as initial therapy by IDSA, but should be considered in specific clinical scenarios in addition to monotherapy; including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. Antibiotic regimens may be altered based on culture results or if infection with a multi drug resistant organism is suspected. These include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum  $\beta$ -lactamase (ESBL)–producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital that carried regional endemics [15]. Cochrane Review recently published an updated guidelines of the choice of antibiotics in patients with FN, with gram-positive bacteria.

An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is not compromised. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured. If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients. Empirical antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and no identified fever source. Per IDSA guidelines, patients with documented Type I hypersensitivity to penicillins may be given ciprofloxacin plus clindamycin or aztreonam plus vancomycin as an alternative. Some low risk patients may be considered for outpatient treatment with oral antibiotics. A combination of ciprofloxacin plus amoxicillin-clavulanate is



recommended as initial empiric therapy. However, quinolones should not be used for empiric therapy in patients taking it for prophylaxis.

For rigorous management of patients who are at risk of this significantly high risk condition, a dedicated team of health care providers familiar with risk-based therapy should monitor and follow-up with outpatient low-risk patients. A management team (e.g., emergency departments, pharmacy, support services) should be accessible 24 h a day. The hospital should also provide transportation for the patient within proximity to the cancer treatment center.

### 45.6.1.3 Antifungal Agents

Invasive fungal infections are most often seen in patients with prolonged neutropenia and after stem-cell transplantation. Empiric antifungal treatment should be considered in patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be greater than 7 days. Choice of agent and duration of therapy is based on the suspected or isolated fungal agent. *Candida* species causes invasive infections most commonly in neutropenic patients, however, patients receiving prophylactic fluconazole, are likely to be infected with fluconazole resistant species like *Candida glabrata* and *Candida krusei*. Oral candidiasis is the most commonly noted fungal infection in patients with breast cancer, and the treatment can also be introduced orally either by oral fluconazole, nystatin [16].

The 2010 IDSA guidelines for empiric antifungal therapy recommend **amphotericin B** deoxycholate, a lipid formulation of amphotericin B, **caspofungin**, **voriconazole**, or **itraconazole** as suitable options for empiric antifungal therapy in neutropenic patients. However, the choice of agent should be based on the suspected infection. For example, caspofungin and other drugs from the echinocandin family should not be used when an invasive aspergillus infection is suspected and lipid formulation of amphotericin b or voriconazole should be preferred instead. Caspofungin, however, is a reasonable choice for suspected candida infections. For persistently febrile patients who have been receiving anti-mold prophylaxis, a different class of antifungal agent with activity against molds should be used for empiric therapy. For example, if **voriconazole** or **posaconazole** has been used for prophylaxis, an **amphotericin B** formulation should be used.

Low risk patients do not require empiric treatment with an antifungal agent as the risk of fungal infection is low in this patient population. Majority of patients who undergo breast cancer treatment do not carry high risk for fungal infection, however given recent surge of new immunotherapy and targeted therapy that may carry different level of risk, providers also should be aware of these possible risks.

#### 45.6.1.4 Antiviral Agents

Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease. However, herpes simplex virus (HSV)–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis. Influenza virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically.

### 45.7 Targeted Therapeutics in Breast Cancer and Neutropenia

Recent advancement of the novel targeted therapeutics in breast cancer, also changed the way we think about neutropenia, FN in patients with breast cancer. Two examples of such agents are CDK 4/6 inhibitors and PARP inhibitors. CDK4/6 inhibitors have been approved as a standard care therapy option for patients with hormone receptor positive breast cancers, either as single agent or combination. Among three FDA approved CDK 4/6 inhibitors, palbociclib and ribociclib showed around 4–7% rate of FN [17–19]. Abemaciclib, which is more specific inhibitor of CDK4, had lower rate of neutropenia and lower rate of febrile neutropenia (1/132), and yet still around 46% patients still experienced various grade of neutropenia [20, 21]. Actual hospitalization and other sequelae related to severe mortality caused by neutropenia from CDK4/6 inhibitors are not as frequent as chemotherapeutics.

Poly ADP ribose polymerase (PARP) inhibitor, is another category of novel targeted therapy that can cause cytopenia, including neutropenia. Given dependency of PARP protein in BRCA defective cancer for the repair of cancer cells when nonhomologous end-joining (NHEJ) DNA repair occurs, PARP inhibitors were studied, and shown efficacy in patients with germline BRCA mutated cancers, including breast cancer [22]. Olaparib was recently approved for its use by FDA [23], and several other PARP inhibitors, such as veliparib, rucaparib, niraparib, and talazoparib are currently under study in breast cancer. The rate of neutropenia of PARP inhibitors, also ranges around 45–50% [24, 25]. It is important for clinicians pay attention to the neutropenia that can be caused by new category of agents that can cause cytopenias. The principle of managing neutropenia caused by these agents is the same, however the detailed guideline of dose management is well established per each agent.

## 45.8 Conclusion

Chemotherapy continues to be a mixed blessing because of its association with myelosuppression and its complications, including chemotherapy-induced neutropenia and febrile neutropenia, a serious medical condition that is prevalent among cancer patients. Management of these side effects is imperative to the health of the patient, and requires clinical and laboratory evaluation, risk assessment, and treatment with empiric broad-spectrum antibiotics. Thanks to improved microbiological laboratory techniques and integration of growth factor usage into the chemotherapy regimens, the mortality directly caused by this condition has been decreasing. However, a dynamic shift of causative organisms secondary to indwelling catheter use, resistance to the antibiotics, new targeted therapy that can cause bone marrow suppression still remain as a challenge for oncologists and patients. Thus, careful risk stratification of patients, proper initial evaluation of condition and treatment history of individual patients, as well as continued development of preventive measure are warranted.

### Multiple Choice Questions

1. What are key features of neutropenic fever?
  - I. Body temperature of greater than 38.5 degrees centigrade
  - II. Three consecutive body temperature readings of greater than 38 degrees centigrade for 2 h
  - III. Decreased number of neutrophils in blood
  - (a) I and II
  - (b) I and III
  - (c) II and III
  - (d) I, II, and III

**Correct answer: B**

**Comments:** For answer II, only two consecutive body temperature readings are necessary.

2. Which of the following accurately describes one grade of severity of febrile neutropenia based on CTCAE guidelines?
  - (a) Grade 1: ANC from the lower normal limit to 1000 cells/mm<sup>3</sup>
  - (b) Grade 2: ANC from 1200 to 750 cells/mm<sup>3</sup>
  - (c) Grade 3: ANC from 1000 to 500 cells/mm<sup>3</sup>
  - (d) Grade 4: ANC < 550 cells/mm<sup>3</sup>

**Correct Answer: C**

**Comments:** Severity is graded as below:

Grade 1: ANC from the lower normal limit to 1500 cells/mm<sup>3</sup>

Grade 2: ANC from 1500 to 1000 cells/mm<sup>3</sup>

Grade 3: ANC from 1000 to 500 cells/mm<sup>3</sup>

Grade 4: ANC < 500 cells/mm<sup>3</sup>

3. What is the suggested guidelines for diagnosing neutropenic fever in breast cancer patients?
- (a) Sustained temperature (>1 h) of greater than 38 degrees centigrade, ANC < 500 cells/ $\mu$ L
  - (b) Sustained temperature (>1 h) of greater than 38 degrees centigrade, ANC < 1000 cells/ $\mu$ L
  - (c) One time reading of 38 degrees centigrade, ANC < 500 cells/ $\mu$ L
  - (d) One time reading of 38 degrees centigrade, ANC < 1000 cells/ $\mu$ L

**Correct Answer:** A

**Comments:** The suggested guidelines are as follows: sustained temperature (>1 h) of greater than 38 degrees centigrade or a one time reading of greater than 38.3 degrees centigrade, ANC < 500 cells/ $\mu$ L. If the ANC < 1000 cells/ $\mu$ L and anticipated to have further drop below 500

4. Common risk factors for developing febrile neutropenia include all of the following except:
- (a) Impaired nutritional status
  - (b) Exposure to dose-dense docetaxel-based regimens
  - (c) Male gender
  - (d) Poor performance status (PS)

**Correct Answer:** C

**Comments:** Females are more at risk for febrile neutropenia than males.

5. What are the primary components of risk assessment for febrile neutropenia? Select all that apply.
- (a) Patient history
  - (b) The patient's age, body temperature, and nutritional status
  - (c) Physical examination
  - (d) Signs and symptoms that determine source of infection

**Correct Answer:** A, C, and D

**Comments:** Answer B is important for evaluating a patient for neutropenic fever, but is not considered primary factors of risk assessment.

6. What is the importance of performing risk assessment on patients with neutropenic fever?
- (a) It can be used to prioritize high-risk patients above low-risk patients when administering treatment
  - (b) It must be performed before diagnosing a patient with febrile neutropenia
  - (c) It can discover co-morbidities that need to be treated before the neutropenic fever
  - (d) It can help determine the type, venue, and duration of antibiotic therapy

**Correct Answer: D**

**Comments:** Proper risk assessment can identify patients as high or low risk, which affects the rigor (type, venue, and duration) of empirical treatment. Comorbidities are also considered when determining treatment, but are not priorities for treatment.

7. What characteristics affect a patient's level of risk, as scored by MASCC? Select all that apply:
- (a) Dehydration
  - (b) Burden and symptoms of febrile neutropenia
  - (c) Age, 55 years
  - (d) Hypertension
  - (e) Fungal infection
  - (f) Pulmonary disease

**Correct Answer: A, B, E, F**

**Comments:** For C, the relevant age is 60 years old. For D, hypotension (systolic blood pressure of 90 mmHg) is important.

8. True or False: The higher the MASCC score, the greater the risk.

**Correct Answer: False**

**Comments:** The lower the MASCC score, the greater the risk.

9. Which of the following regarding laboratory tests is false?
- (a) Complete blood cell (CBC) count with differential leukocyte count and platelet count should be performed
  - (b) Chemistry panel should be performed
  - (c) At least two blood cultures are recommended, to be collected consecutively
  - (d) A chest radiograph should be ordered for patients with respiratory symptoms

**Correct Answer: C**

**Comments:** At least two sets of blood cultures are recommended, with each set collected simultaneously from each lumen of an existing central venous catheter (CVC), or from two separate venipunctures if no central catheter is present.

10. What are the guidelines for treating high risk patients with febrile neutropenia? Select all that apply.
- (a) Hospitalization for empirical broad spectrum intravenous antibiotic therapy
  - (b) Steroid treatment to reduce fever symptoms
  - (c) Low threshold of suspicion for patients who do not present with fever but develop septicemia
  - (d) If no source of infection is found, treatment should be continued until recovery of ANC to  $>500$  cells/mm<sup>3</sup>

**Correct Answer:** A, C, and D

**Comments:** Answer B is not a treatment of febrile neutropenia. However, steroids may make diagnosis of febrile neutropenia in neutropenia patients more difficult since it masks fever symptoms.

11. Which of the following drugs is not categorized as a monotherapy with a broad spectrum, anti-pseudomonal, beta lactam drug?
- (a) Cefepime
  - (b) Carabapenem
  - (c) Piperacillin-tazobactam
  - (d) Ciprofloxacin

**Correct Answer:** D

**Comments:** Ciprofloxacin is an orally ingested antibiotic that is used as an alternative to penicillin on clinically stable patients with Type I hypersensitivity to penicillins.

12. What is the most common cause of infection among patients with febrile neutropenia?
- (a) Gram-positive bacteria
  - (b) Gram-negative bacteria
  - (c) Fungi
  - (d) Virus

**Correct Answer:** B

**Comments:** Gram-negative bacteria, specifically coagulase negative Staphylococci, are the most frequently identified organisms from blood cultures. However, the incidence of multi drug resistant gram-negative organisms as well as gram-positive bacteria are on the rise.

13. Which of the following matches the infectious agent with the correct mechanism of infection?
- (a) Fungi, indwelling infusion catheters
  - (b) Gram-negative bacteria, breached mucosa of GI tract
  - (c) Virus, indwelling infusion catheters
  - (d) Gram-positive bacteria, indwelling infusion catheters

**Correct Answer:** B

**Comments:** Gram-positive bacteria infect through increased and prolonged use of indwelling infusion catheters. Fungal and viral infections are common in patients with prolonged neutropenia and a history of multiple chemotherapeutic uses.

14. True or False: The risk of fungal infection increases only with the duration and severity of neutropenia.

**Correct Answer:** False

**Comments:** Risk of fungal infection also increases with prolonged use of antibiotics and the number of chemotherapy cycles given.

15. 56 years old female with stage IIB ER/PR low positive and HER2 negative left breast cancer is undergoing dose dense AC (Adriamycin and cyclophosphamide) therapy in an adjuvant setting. After the second cycle, she visited emergency center with persistent fever of 39 °C over 2 h. She denies cough, chest pain, shortness of breath, diarrhea, or abdominal pain. She is receiving hydration and basic work ups. Which of the following belong to recommended basic work up?

- I. Blood and urine culture
  - II. Comprehensive chemistry panel
  - III. Chest X ray
  - IV. Arterial blood gas analysis
- (a) I and II
  - (b) I and III
  - (c) II and III
  - (d) I, II, and III

**Correct Answer: D**

**Comments:** Arterial blood gas analysis does not apply in this scenario given her negative respiratory symptoms. Basic work ups include blood and urine culture, chest X ray, complete blood count, and comprehensive chemistry panel.

16. Same patient from question #15, is complete with basic blood work. Her absolute neutrophil count is around 750 K/ $\mu$ L. The emergency center resident calls you to ask for a guidance on the choice of antibiotics. She has a medi-port to receive chemotherapy. Otherwise, physical exam is unremarkable except mucositis, and the surgical wound from her lumpectomy is well healed. Patient reports a penicillin allergy. Which antibiotics would you recommend?

- I. Cefepime 2 g IV q8h
  - II. Piperacillin-tazobactam 4.5 g IV q6h
  - III. Vancomycin 15 mg/kg IV q12h
  - IV. Flagyl 500 mg IV q8h
- (a) I and II
  - (b) I and III
  - (c) II and III
  - (d) I, II, and III

**Correct Answer: B**

**Comments:** While both cefepime and piperacillin-tazobactam can be first choice of gram-negative coverage, the patient has a penicillin allergy which makes the cefepime as a first choice. There could be a still cross-reactivity between penicillin allergy and cefepime. Since the patient has a mucositis, and risk of catheter-mediated infection, additional gram positive coverage with vancomycin is recommended.

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# Chapter 46

## Chemotherapy Induced Nausea and Vomiting



Rudolph M. Navari

**Abstract** Oncology practitioners currently have very effective antiemetic agents in the form of 5-hydroxytryptamine-3 receptor antagonists, neurokinin-1 receptor antagonists, dexamethasone, and olanzapine for use in the prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy. The choice of individual agents and the combination of agents should be dictated by the emetogenicity of the chemotherapy and patient risk factors. The available agents for the prevention of CINV appear to be safe and effective with few reported adverse events when used in the recommended doses.

The use of these agents in various clinical settings is described by established antiemetic guidelines from the Multinational Association of Supportive Care in Cancer and the European Society of Medical Oncology, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network. These guidelines should be followed by practitioners in order to provide the highest possible quality of care for patients receiving chemotherapy.

**Keywords** Nausea · Emesis · Chemotherapy · Antiemetics

### Abbreviations

ASCO	American Society of Clinical Oncology
CINV	Chemotherapy-induced nausea and vomiting
CTZ	Chemoreceptor trigger zone
FDA	Food & Drug Administration

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GI	Gastrointestinal
5-HT <sub>3</sub>	5-hydroxytryptamine-3
HEC	Highly emetogenic chemotherapy
MEC	Moderately emetogenic chemotherapy
MASCC	Multinational Association of Supportive Care in Cancer
NCCN	National Comprehensive Cancer Network
NTS	Nucleus Tractus solitarius
NK-1	Neurokinin-1
VAS	Visual analogue scale
VC	Vomiting Centre

## 46.1 Introduction

Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment [1–3]. Increased risk of CINV is associated with the type of chemotherapy administered (Table 46.1) and specific patient characteristics (Table 46.2) [3]. CINV can result in serious complications, such as weakness, weight loss, electrolyte imbalance, dehydration or anorexia, and is associated with a variety of complications, including fractures, oesophageal tears, decline in behavioural and mental status, and wound dehiscence [1–3]. Patients who are dehydrated, debilitated or malnourished, as well as those who have an electrolyte imbalance or those who have recently undergone surgery or radiation therapy are at greater risk of experiencing serious complications from CINV [1–3].

The type of chemotherapy to be given defines the degree of emetogenicity (Table 46.3) and the risk of CINV for patients. Table 46.4, 46.5 and 46.6 lists the emetogenicity of the various intravenous chemotherapy agents. Table 46.7 lists the emetogenicity of some of the oral chemotherapy agents. The type and number of

**Table 46.1** Emetic potential of chemotherapy agents

Emetogenic potential	Typical agents	Definition (no CINV prevention)
High	Cisplatin, dacarbazine, melphalan (high dose), nitrogen mustard, cyclophosphamide plus an anthracycline	Emesis in nearly all patients
Moderate	Anthracyclines, carboplatin, carmustine (high dose), cyclophosphamide, ifosfamide, irinotecan, methotrexate (high dose), oxaliplatin, topotecan	Emesis in >70% of patients
Low	Etoposide, 5-fluorouracil, gemcitabine, mitoxantrone, taxanes, vinblastine, vinorelbine	Emesis in 10–70% of patients
Minimal	Bortezomib, hormones, vinca alkaloids, bleomycin	Emesis in <10% of patients

*CINV* chemotherapy-induced nausea and vomiting

**Table 46.2** Patient-related risk factors for emesis following chemotherapy

Major factors	Minor factors
Female, Age < 50 years History of low prior chronic alcohol intake (<1 ounce of alcohol/day) History of previous chemotherapy-induced emesis, Emetogenicity of chemotherapy regimen	History of motion sickness, Emesis during past pregnancy

**Table 46.3** Chemotherapy emetogenicity risk classification

Risk classification	Definition
High emetic risk	>90% frequency of emesis
Moderate emetic risk	30–90% frequency of emesis
Low emetic risk	10–30% frequency of emesis
Minimal emetic risk	<10% frequency of emesis

**Table 46.4** Highly emetogenic chemotherapy

>90% emetic risk:
Anthracycline + cyclophosphamide combination (defined as either doxorubicin or epirubicin with cyclophosphamide)
Carboplatin AUC $\geq 4$
Carmustine $>250 \text{ mg/m}^2$
Cisplatin
Cyclophosphamide $>1500 \text{ mg/m}^2$
Dacarbazine
Doxorubicin $\geq 60 \text{ mg/m}^2$
Epirubicin $>90 \text{ mg/m}^2$
Ifosfamide $\geq 2 \text{ g/m}^2$ per dose
Streptozocin

**Table 46.5** Moderately emetogenic chemotherapy

30–90% emetic risk:
Bendamustine
Oxaliplatin
Carboplatin AUC <4
Carmustine $\leq 250 \text{ mg/m}^2$
Cyclophosphamide $\leq 1500 \text{ mg/m}^2$
Ifosfamide <2 g/m <sup>2</sup> per dose
Irinotecan
Cytarabine >200 mg/m <sup>2</sup>
Doxorubicin <60 mg/m <sup>2</sup> , daunorubicin, idarubicin
Temozolomide
Methotrexate $\geq 250 \text{ mg/m}^2$

**Table 46.6** Low emetogenic chemotherapy

10–30% emetic risk:
5-fluorouracil
Ado-trastuzumab emtansine
Cytarabine (low dose) 100– 200 mg/m <sup>2</sup>
Docetaxel
Eribulin
Gemcitabine
Topotecan
Paclitaxel
Pemetrexed
Ziv-aflibercept
Vismodegib

**Table 46.7** Oral chemotherapy agents with moderate to high emetogenic potential

Altretamine
Busulfan ( $\geq 4 \text{ mg/d}$ )
Ceritinib
Crizotinib
Cyclophosphamide ( $\geq 100 \text{ mg/m}^2/\text{d}$ )
Estramustine
Etoposide
Lenvatinib
Lomustine (single day)
Mitotane
Olaparib
Panobinostat
Procarbazine
Temozolomide ( $>75 \text{ mg/m}^2/\text{d}$ )

antiemetics to be used for the control of CINV is dictated by whether the chemotherapy is of high, moderate, or low emetogenic potential.

Studies have suggested that physicians and nursing staff underestimated the CINV experienced by patients [4], and there is a significant financial impact of health care expenditures when CINV is not well controlled [5].

The use of first generation 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonists plus dexamethasone has improved the control of CINV [3, 6]. Studies have also demonstrated improvement in the control of CINV with the use of a second-generation 5-HT<sub>3</sub> receptor antagonist palonosetron [7], neurokinin-1 (NK-1) receptor antagonists (aprepitant, netupitant, and rolapitant) [8–10] and olanzapine, an antipsychotic that blocks multiple neurotransmitters in the central nervous system [11–15].

The primary endpoint used for studies evaluating various agents for the control of CINV has been complete response (no emesis, no use of rescue medication) over the acute (24 h post-chemotherapy), delayed (24–120 h) and overall (0–120 h) periods [3]. Studies have shown that the combination of a 5-HT<sub>3</sub> receptor antagonist, dexamethasone and an NK<sub>1</sub> receptor antagonist have improved the control of emesis in patients receiving either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) over a 120-h period following chemotherapy administration [3, 7–13]. Many of these same studies have measured nausea as a secondary endpoint and have demonstrated that nausea has not been well controlled [16, 17].

Emesis is a well-defined event that is easily measured, but nausea may be more subjective and more difficult to measure. However, two well defined measures of nausea that appear to be effective and reproducible measurement tools are the visual analogue scale (VAS) and the Likert Scale [18]. The VAS is a scale from 0 to 10 or 0 to 100, with zero representing no nausea and 10 or 100 representing maximal nausea. The Likert Scale asks patients to rate nausea as ‘None, Mild, Moderate or Severe’.

Many studies have reported the secondary endpoint of ‘no significant nausea’ or ‘only mild nausea [3, 8, 17]. Studies that have reported ‘no nausea’ may be more useful in identifying the most effective available anti-nausea agents [14, 16].

Despite the introduction of more effective antiemetic agents, emesis and nausea remain a significant complication of chemotherapy. The purpose of this review is to evaluate the clinical agents available for the prevention and treatment of CINV. The use of these agents in various clinical settings is described using the recently established guidelines from the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society of Medical Oncology [19], the American Society of Clinical Oncology (ASCO) [20], and the National Comprehensive Cancer Network (NCCN) guidelines [21]. The literature cited in the report consists of the primary clinical trials used for the United States Food & Drug Administration (FDA) approval of the various agents as well as recent comprehensive reviews.



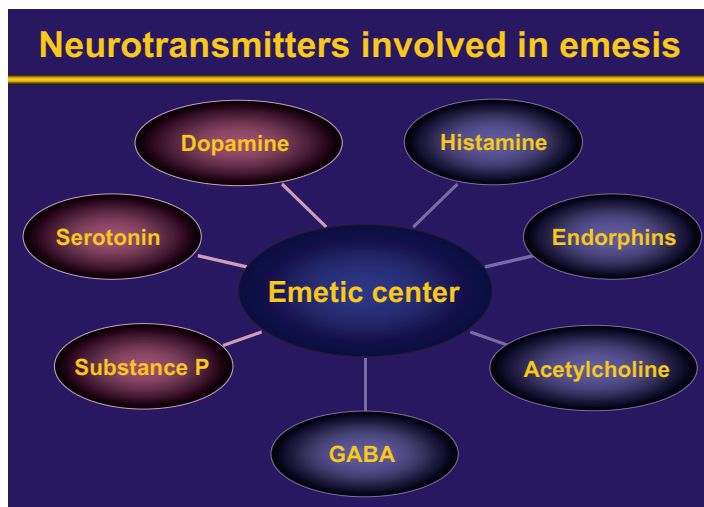


Fig. 46.2 Neurotransmitters Involved in Emesis

formation of the medulla, which coordinates the mechanism of nausea and vomiting. An additional important area, also located in the medulla, is the CTZ in the area postrema near the fourth ventricle [22]. It is strongly suspected that the nucleus tractus solitarius (NTS) neurons lying ventrally to the area postrema initiate emesis [23]. This medullary area is a convergence point for projections arising from the area postrema and the vestibular and vagal afferents [23]. The NTS is a good candidate for the site of action of centrally acting antiemetics.

The main approach to the control of emesis has been to identify the active neurotransmitters and their receptors in the central nervous system and the GI tract that mediate the afferent inputs to the VC (Fig. 46.2). Agents that may block these neurotransmitter receptors in the CTZ, the VC or the GI tract may be useful in preventing or controlling emesis (Table 46.8).

Nausea is a difficult-to-describe, sick or queasy sensation, usually perceived as being in the stomach that is sometimes followed by emesis [18]. The experience of nausea is difficult to describe in another person. Nausea and emesis are not neces-

Table 46.8 Antiemetic receptor antagonists

Dopamine receptor antagonists	5-HT <sub>3</sub> receptor antagonists	Dopa-5-HT <sub>3</sub> receptor antagonists	NK <sub>1</sub> receptor antagonists
Butyrophenones, olanzapine, phenothiazines	Azasetron, dolasetron (not recommended for use per US FDA), granisetron, olanzapine, ondansetron (IV dose restriction per FDA), palonosetron, ramosetron, tropisetron	Metoclopramide	Aprepitant (MK-869), fosaprepitant, netupitant, rolapitant)

IV intravenous, NK neurokinin, 5-HT<sub>3</sub> serotonin



sarily on a continuum. One can experience nausea without emesis and one can have sudden emesis without nausea. Nausea has been assumed to be the conscious awareness of unusual sensations in the 'vomiting centre' of the brainstem (Fig. 46.1), but the existence of such a centre and its relationship to nausea remain controversial [18].

The study of the receptors that are illustrated in Fig. 46.2 has guided the development of the antagonists to the serotonin and the substance P receptors with relative success in controlling emesis. It is not clear whether the serotonin and/or the substance P receptors are important in the control of nausea. Other receptors, such as dopaminergic, histaminic and muscarinic, may be the dominant receptors in the control of nausea [3, 16, 17].

### **46.1.2 Types of Chemotherapy-Induced Nausea and Vomiting (CINV)**

Five categories are used to classify CINV: acute, delayed, anticipatory, breakthrough, and refractory. Nausea and vomiting may occur any time after the administration of chemotherapy, but the mechanisms appear different for CINV occurring in the first 24 h after chemotherapy in contrast to that which occurs in the period of 1–5 days after chemotherapy.

#### **46.1.2.1 Acute CINV**

The term acute-onset CINV refers to nausea and/or vomiting occurring within 24 h of chemotherapy administration [3] and usually peaks within the first 5, 6 h after the initiation of chemotherapy. The incidence of acute emesis and/or nausea reflects several treatment-related factors, including the environment in which chemotherapy is administered, the emetogenicity of the chemotherapy, the dosage of the emetogenic agents and patient-related factors [21].

#### **46.1.2.2 Delayed CINV**

Nausea and/or vomiting that develop more than 24 h after chemotherapy administration is known as delayed emesis and/or nausea. Typically occurring with administration of cisplatin, carboplatin, doxorubicin, or cyclophosphamide, delayed emesis/nausea is more common in those who experience acute emesis/nausea. Other predictive factors include the dose and the emetogenicity of the

chemotherapeutic agent, patient sex and age, and protection against nausea and vomiting in previous cycles of chemotherapy [3, 21]. For cisplatin, which has been most extensively studied, delayed emesis reaches peak intensity 2–3 days subsequent to chemotherapy administration and can last up to a week [3, 19–21].

#### **46.1.2.3 Breakthrough CINV**

Vomiting and/or nausea that occurs within 5 days after chemotherapy despite prophylactic use of antiemetic agents and/or requires additional antiemetics ('rescue') is called breakthrough emesis

#### **46.1.2.4 Refractory CINV**

Vomiting and/or nausea occurring after chemotherapy in subsequent chemotherapy cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles is known as refractory emesis [3, 21].

#### **46.1.2.5 Anticipatory CINV**

If patients experience CINV, they may develop a conditioned response known as anticipatory nausea and/or vomiting, which occurs prior to the administration of chemotherapy in future chemotherapy cycles and is attributed to the adverse memory of prior CINV. Incidence rates for this type of nausea and vomiting range from 10% to 45%, with nausea occurring more frequently [3, 21].

## **46.2 Antiemetic Agents**

### ***46.2.1 Dopamine Receptor Antagonists***

Dopamine receptors are known to exist in the CTZ, and this is the main area of activity of the dopamine antagonists, such as the phenothiazines and the butyrophenones (droperidol, haloperidol). However, a high level of blockade of the dopamine receptors results in extrapyramidal reactions, as well as disorientation and sedation, limiting the clinical use of these agents. Their current use is primarily to treat established nausea and emesis and not for CINV prophylaxis [21].

### 46.2.2 Serotonin (5-HT<sub>3</sub>) Receptor Antagonists

Serotonin receptors, specifically the 5-HT<sub>3</sub> receptors, exist in the central nervous system and in the GI tract. The 5-HT<sub>3</sub> receptor antagonists appear to act through both the central nervous system and the GI tract via the vagus and splanchnic nerves.

The introduction of 5-HT<sub>3</sub> receptor antagonists for the prevention of CINV, as well as post-operative and radiotherapy-induced nausea and vomiting, has resulted in an improvement in supportive care [3]. Treatment guidelines for the prevention of CINV recommended by a number of international groups [19–21] suggest the use of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone alone or in combination with other antiemetics pre-chemotherapy for the prevention of acute CINV, and the use of dexamethasone alone or in combination with other antiemetics following chemotherapy for the prevention of delayed nausea and vomiting in patients receiving either moderately or highly emetogenic chemotherapy.

### 46.2.3 First-Generation 5-HT<sub>3</sub> Receptor Antagonists

Table 46.9 shows the 5-HT<sub>3</sub> receptor antagonists currently in use. The first-generation 5-HT<sub>3</sub> receptor antagonists (dolasetron, granisetron, ondansetron, tropisetron [24], azasetron [25] and ramosetron [26] are equivalent in efficacy and toxicities when used in the recommended doses and compete only on an economic basis [27]. They have not been associated with major toxicities, with the most commonly reported adverse events being mild headache, constipation and, occasionally, mild diarrhea [3]. Azasetron and ramosetron are not available in North America and

**Table 46.9** Serotonin antagonists and dosage before chemotherapy<sup>a</sup>

Antiemetic	Route	Dosage
Azasetron	IV	10 mg
Dolasetron <sup>b</sup>	IV	100 mg or 1.8 mg/kg
	PO	100 mg
Granisetron	IV	10 µg/kg or 1 mg or 500 mg sc
	PO	2 mg (or 1 mg twice daily)
Ondansetron	IV	8 mg (restricted to <16 mg)
	PO	24 mg
Palonosetron	IV	0.25 mg
Ramosetron	IV	0.30 mg
Tropisetron	IV or PO	5 mg

IV intravenous, PO oral

<sup>a</sup>The same doses are used for highly and moderately emetogenic chemotherapy

<sup>b</sup>Not recommended for use per US FDA

Europe and have not been compared extensively with the other 5-HT<sub>3</sub> receptor antagonists. They are marketed primarily in Southeast Asia.

Differences in metabolism of the 5-HT<sub>3</sub> receptor antagonists may occur due to genetic variability in individuals which may lead to a difference in response to these agents, but there have been no documented clinical reports of this phenomenon [3, 19–21, 24–27].

In 2006, Canada issued a drug alert for dolasetron, due to the potential of serious cardiovascular adverse events (cardiac arrhythmias) [28], stating that dolasetron was not indicated for use in children, but only for prevention of CINV in adults [28]. Subsequently, in 2010, the US FDA announced that the intravenous form of dolasetron should no longer be used to prevent CINV in any patient. New data suggested that dolasetron injection can increase the risk of developing a prolongation of the QT interval, which may potentially precipitate life-threatening ventricular arrhythmias [29].

In 2012, the FDA placed a restriction on the doses of intravenous ondansetron due to the risk of prolongation of the QT interval [30]. Patients who may be at particular risk for QT prolongation with ondansetron is those with congenital long QT syndrome, congestive heart failure, brady-arrhythmias, or patients taking concomitant medications that prolong the QT interval. The use of a single 32-mg intravenous dose of ondansetron should be avoided. New information indicates that QT prolongation occurs in a dose-dependent manner, and specifically at a single intravenous dose of 32 mg. The lower-dose intravenous regimen of 0.15 mg/kg every 4 h for three doses may be used in adults with CINV. However, no single intravenous dose of ondansetron should exceed 16 mg due to the risk of QT prolongation. The new information does not change any of the recommended oral dosing regimens for ondansetron, including the single oral dose of 24 mg for CINV [30].

Mason et al. [31] has reported that intravenous granisetron had no clinically significant effect on the QTc interval at supratherapeutic concentrations.

The first-generation 5-HT<sub>3</sub> receptor antagonists have not been as effective against delayed emesis as they are against acute CINV [32–34]. The first-generation 5-HT<sub>3</sub> receptor antagonists alone do not add significant efficacy to that obtained by dexamethasone in the control of delayed emesis [33]. Hickok et al. [34] reported that the first-generation 5-HT<sub>3</sub> receptor antagonists used in the delayed period were no more effective than prochlorperazine in controlling nausea. The antiemetic effects of prochlorperazine can be attributed to post-synaptic dopamine receptor blockade in the CTZ. A meta-analysis [33] showed that there was neither clinical evidence nor considerations of cost effectiveness to justify using the first-generation 5-HT<sub>3</sub> receptor antagonists beyond 24 h after chemotherapy for the prevention of delayed emesis. A number of studies have also demonstrated that there has been poor control of delayed nausea by the first-generation 5-HT<sub>3</sub> receptor antagonists in patients receiving HEC or MEC [12, 35, 36].

#### 46.2.4 *Extended Release Granisetron*

A randomized, double-blind, phase III clinical trial evaluated the antiemetic efficacy of transdermal granisetron compared to oral granisetron in patients receiving MEC and HEC [37]. There was no significant difference in the control of acute or delayed emesis between transdermal and oral granisetron. The data demonstrated that transdermal granisetron was effective and safe in the control of acute emesis induced by MEC and HEC [37].

APF530 is a new, subcutaneously (SC) administered polymeric formulation of granisetron that was developed to provide slow, controlled, and sustained release of granisetron to prevent both acute and delayed CINV associated with MEC and HEC [38]. APF530 consists of 2% granisetron and a polymer vehicle of tri(ethylene glycol) poly(orthoester) (TEG-POE) that undergoes controlled hydrolysis, resulting in slow, controlled, and sustained drug release. The novel biodegradable polymeric excipient is hydrolyzed *in vivo*, generating nontoxic biodegradable metabolites. This Biochronomer™ drug delivery system (Heron Therapeutics, Inc., Redwood City, CA) allows therapeutic levels of granisetron to be maintained for >5 days with a single subcutaneous injection. In a clinical study [38] in patients undergoing chemotherapy, single-dose APF530 (5–15 mg granisetron) administered SC in the abdomen provided circulating levels of granisetron within 30 min, a maximum plasma concentration at ~24 h, and sustained therapeutic levels for >120 h. In a phase 3 noninferiority trial, the clinical efficacy of APF530 250 and 500 mg SC (containing granisetron 5 and 10 mg, respectively) was compared with that of the approved dose of palonosetron (0.25 mg intravenously) in combination with dexamethasone for prevention of acute and delayed CINV following single-day administration of MEC or HEC in patients with cancer. APF530 was noninferior to palonosetron with injection site reactions and constipation the most commonly reported adverse events [38]. In a QTc study, the APF530 formulation had no clinically significant effect on the QTc interval at supratherapeutic concentrations [31].

#### 46.2.5 *Second-Generation 5-HT<sub>3</sub> Receptor Antagonists: Palonosetron*

Palonosetron is a second-generation 5-HT<sub>3</sub> receptor antagonist that has antiemetic activity at both central and GI sites [3, 6, 7]. In comparison with the first-generation 5-HT<sub>3</sub> receptor antagonists, it has a higher potency, a significantly longer half-life and a different molecular interaction with 5-HT<sub>3</sub> receptors [3, 6, 7, 39] (Table 46.10). Palonosetron studies suggest that it may have efficacy in controlling delayed CINV compared with the first-generation 5-HT<sub>3</sub> receptor antagonists [3, 6, 7, 39].

Palonosetron demonstrated a 5-HT<sub>3</sub> receptor binding affinity at least 30-fold higher than other 5-HT<sub>3</sub> receptor antagonists [34]. Rojas et al. [40] reported that palonosetron exhibited allosteric binding and positive cooperativity when binding

**Table 46.10** 5-HT<sub>3</sub> receptor antagonists' binding affinity and plasma half-life

Drug	pKi [-log(Ki)]	Half-life (hours)
Palonosetron	10.45	40
Ondansetron	8.39	4
Granisetron	8.91	9
Dolasetron+	7.60	7.3

+ Half-life reported for hydrodolasetron, the active metabolite of dolasetron

to the 5-HT<sub>3</sub> receptor compared with simple bimolecular binding for both granisetron and ondansetron. Additional studies by Rojas et al. [40] suggested that palonosetron triggers 5-HT<sub>3</sub> receptor internalization and causes prolonged inhibition of receptor function. Differences in binding and effects on receptor function may explain some differences between palonosetron and the first-generation 5-HT<sub>3</sub> receptor antagonists [7, 40]. These differences may explain palonosetron's efficacy in delayed CINV compared with the first-generation receptor antagonists [3, 7, 39].

In a systematic review and meta-analysis of all randomized controlled trials comparing a single dose of palonosetron with other 5-HT<sub>3</sub> receptor antagonists, Botrel et al. [41] concluded that palonosetron was more effective than the first generation receptor antagonists in preventing acute and delayed CINV in patients receiving MEC or HEC, regardless of the use of concomitant corticosteroids. Schwartzberg et al. [42] concluded that palonosetron is more effective than the first generation 5-HT<sub>3</sub> receptor antagonists in controlling CINV in the delayed and overall post-chemotherapy periods based on a pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron. In an additional review, Popovic et al. [43] concluded that palonosetron is safer and more efficacious than the other 5-HT<sub>3</sub> receptor antagonists. The international antiemetic guidelines [19–21] recommend palonosetron as the preferred 5-HT<sub>3</sub> receptor antagonist.

The safety and tolerability of palonosetron has been well documented in multiple, large phase III trials. There were no clinically relevant differences seen among palonosetron, ondansetron, or dolasetron in laboratory, electrocardiographic, or vital sign changes over multiple cycles of chemotherapy [7, 39, 43–45]. The adverse reactions reported were the most common reactions reported for the 5-HT<sub>3</sub> receptor antagonist drug class. There have been no reports of any adverse cardiac events with palonosetron, specifically no prolongation of the QT interval in healthy volunteers or patients receiving repeated cycles of emetogenic chemotherapy [7, 39, 43–45] Table 46.11 summarizes the reported adverse events of the antiemetic guideline directed serotonin antagonists.

There are no other second-generation 5-HT<sub>3</sub> receptor antagonists on the market and there is no information available on other second-generation agents in development.

**Table 46.11** Safety and tolerability of the antiemetic guideline directed serotonin antagonists [19–21, 30, 31]

Antiemetic	Route	Adverse events
Granisetron	IV, PO	Constipation, headache, diarrhea, mild dizziness
Ondansetron	IV, PO	Constipation, headache, diarrhea, mild dizziness, QT <sub>c</sub> prolongation with IV doses >16 mg
Palonosetron	IV, PO	Constipation, headache, diarrhea

### 46.2.6 Dopamine-Serotonin Receptor Antagonists

Metoclopramide has antiemetic properties both in low doses as a dopamine antagonist and in high doses as a serotonin antagonist. The use of metoclopramide may be somewhat efficacious in relatively high doses (20 mg orally, three times daily) in the delayed period [46] but may result in sedation and extrapyramidal side effects [3, 21, 47].

Metoclopramide has been used both as a preventative agent for CINV [46] as well as a treatment for breakthrough CINV [21, 47].

In 2013, the European Medicines Agency issued use restrictions for metoclopramide due to the risk of

- extrapyramidal disorders
- involuntary movement disorders that may include muscle spasms
- tardive dyskinesia

It was noted that the risk of side effects is increased at high doses or with long-term treatment. The review recommended that treatment duration be restricted to short-term use (up to 5 days) and that the maximum dose be limited in adults to 10 mg three times daily. It was also recommended that metoclopramide not be used in children under 1 year old [48].

The reduced dose of 10 mg three times daily may be less efficacious as a preventative agent for CINV and as a treatment for breakthrough CINV [3, 21, 46, 47].

### 46.2.7 Neurokinin (NK-1) Receptor Antagonists

Substance P is a mammalian tachykinin that is found in vagal afferent neurons innervating the brainstem NTS, which sends impulses to the VC [49]. Substance P induces vomiting and binds to NK<sub>1</sub> receptors in the abdominal vagus, the NTS, and the area postrema [49]. Compounds that block NK<sub>1</sub> receptors lessen emesis after cisplatin, ipecac, apomorphine and radiation therapy [49]. These observations have recently led to the development of NK<sub>1</sub> receptor antagonists and the study of the role they may play in controlling CINV.

### 46.2.7.1 Aprepitant

Aprepitant is an NK-1 receptor antagonist that blocks the emetic effects of substance P [3, 8, 50]. When combined with a standard regimen of the corticosteroid dexamethasone and a 5-HT<sub>3</sub> receptor antagonist, aprepitant is effective in the prevention of CINV in patients receiving cisplatin based HEC [3, 50]. This regimen is recommended in the guidelines of multiple international groups for the control of CINV in patients receiving HEC [19–21].

Combined data from two large phase III trials of aprepitant plus a first-generation 5-HT<sub>3</sub> receptor antagonist and dexamethasone for the prevention of CINV in patients receiving HEC demonstrated an improvement in complete response when aprepitant was added to ondansetron and dexamethasone, but there was no improvement in nausea when the pooled data was analysed for sex (no nausea, overall period: 46% for women, aprepitant group, 38% for women, control group; 50% for men, aprepitant group, 44% for men, control group) [51]. Using the same pooled data, a separate analysis [52] showed a statistical but small improvement in no nausea with the use of aprepitant (no nausea, overall period: 48%, aprepitant group; 42%, control group).

In a similar study involving breast cancer patients receiving cyclophosphamide and doxorubicin or epirubicin, aprepitant was added to ondansetron and dexamethasone for the prevention of CINV. The addition of aprepitant to the 5-HT<sub>3</sub> receptor antagonist plus dexamethasone improved the complete response, but there was no improvement in nausea (no nausea, overall period: 33% aprepitant group; 33% control group) [36].

Palonosetron and aprepitant have been combined with dexamethasone for the prevention of CINV in a phase II study of 58 patients who received doxorubicin and cyclophosphamide [53]. This three-drug antiemetic regimen was found to be safe and highly effective in preventing emesis and rescue in the acute, delayed and overall periods, but there was poor control of nausea (no nausea, overall period: 30%).

### 46.2.7.2 Fosaprepitant

Fosaprepitant (also known as MK-0517 and L-758,298) is a water-soluble phosphoryl pro-drug for aprepitant that, when administered intravenously, is converted to aprepitant within 30 min via the action of ubiquitous phosphatases. The pharmacological effect of fosaprepitant is attributed to aprepitant. Due to the rapid conversion of fosaprepitant to the active form (aprepitant) by phosphatase enzymes, it is expected to provide the same aprepitant exposure in terms of area under the curve (AUC) and a correspondingly similar antiemetic effect [54, 55]. Studies have demonstrated that a single dose of intravenous fosaprepitant, 150 mg on day 1 of cisplatin chemotherapy, was noninferior to a 3-day oral regimen of aprepitant in the prevention of CINV in the 120 h post-chemotherapy [55].

Both standard 3-day dosing of aprepitant and single-dose fosaprepitant have been demonstrated to be well tolerated after ondansetron and dexamethasone in



patients receiving cisplatin [55]. The tolerability profiles of the two regimens were similar, except for a higher incidence of infusion-site adverse events and significantly more thrombophlebitis with intravenous fosaprepitant. Higher incidence of infusion-site adverse events was observed in a retrospective review of 98 patients treated with fosaprepitant [56].

Aprepitant is metabolized extensively by liver enzymes, primarily CYP3A4. CYP3A4 inhibitors can increase aprepitant exposure, and CYP3A4 inducers can reduce aprepitant exposure [57]. Aprepitant is also both an inducer and a moderate inhibitor of CYP3A4 [58]. Consequently, the potential for drug-drug interactions exists when aprepitant is coadministered with other drugs that are metabolized by CYP enzymes, including chemotherapeutic agents [59]. Results from several clinical efficacy trials and pharmacokinetic studies showed that most drug-drug interactions with aprepitant had little or no clinical consequence and that no differences in severe adverse events were noted between treatment arms with or without aprepitant [52, 59]. Aprepitant had minimal effect on the area under the curve (AUC) of several chemotherapeutic agents tested, including cyclophosphamide, docetaxel, and vinorelbine [59]. Coadministration of aprepitant causes a significant increase in the AUC of some corticosteroids, including a 2.2-fold increase in dexamethasone and a 2.5-fold increase in oral methylprednisolone, necessitating up to 50% dose reduction of these drugs [59]. Aprepitant causes reduced AUC of oral contraceptives, and this has prompted the recommendation of a secondary barrier contraceptive for patients receiving aprepitant [59]. Ifosfamide and aprepitant are both substrates of CYP3A4, and theoretical questions have been raised as to whether aprepitant could be potentially involved in rare cases of ifosfamide encephalopathy, but no clinical data exist demonstrating an association [8, 57, 59].

Recently, the success of the use of NK-1 receptor antagonists with 5-HT<sub>3</sub> receptor antagonists and dexamethasone in preventing emesis in patients receiving single day highly emetogenic chemotherapy [3, 6] prompted the use of the NK-1 receptor antagonist aprepitant combined with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone in patients receiving multi-day, high dose chemotherapy prior to SCT. A number of Phase III studies have been reported with the use of the NK-1 aprepitant added to a 5-HT<sub>3</sub> receptor antagonists and dexamethasone [60–63] in patients receiving multi-day, high dose chemotherapy prior to autologous or allogeneic stem cell transplant (SCT). In a randomized, placebo-controlled, phase III clinical trial, Stiff et al. [62] randomized 179 patients receiving multi-day, high dose chemotherapy prior to SCT for autologous and allogeneic transplants to aprepitant or placebo in combination with ondansetron and dexamethasone prior to chemotherapy. There was a significant improvement in emesis with the use of aprepitant, but no difference in the use of rescue medications or nausea. No adverse events were noted with the use of aprepitant.

Schmitt et al. [60] randomized 362 patients receiving 2 days of high dose melphalan chemotherapy prior to SCT for autologous transplants to aprepitant or placebo in combination with granisetron and dexamethasone prior to chemotherapy and post chemotherapy. There was a significant improvement in complete response with the use of aprepitant, but no difference in the use of rescue medications or

nausea. No adverse events were noted with the use of aprepitant. Svanberg and Birgegard [63] randomized 96 patients receiving multi-day, high dose chemotherapy prior to SCT for autologous transplants to aprepitant or placebo in combination with tropisetron and a corticosteroid prior to chemotherapy and post chemotherapy. There was a significant improvement in emesis with the use of aprepitant, but no difference in the use of rescue medications or nausea. No adverse events were noted with the use of aprepitant.

Pielichowski et al. [61] used aprepitant, palonosetron, and dexamethasone to prevent nausea and vomiting following BEAM chemotherapy before autologous hematopoietic stem cell transplantation for patients with non-Hodgkin's or Hodgkin's lymphoma. Emesis was improved in the acute and delayed phases post chemotherapy compared to historical controls who received ondansetron or palonosetron plus dexamethasone alone.

One retrospective study and two prospective (phase II, III) studies, each with a small number of patients (25–40 patients) also demonstrated improvement in emesis with the addition of aprepitant to a 5-HT<sub>3</sub> receptor antagonist with or without a corticosteroid in patients receiving autologous or allogeneic stem cell transplant [64–66].

As a result of the studies cited above, the 2017 ASCO and the 2017 MASCC/ESMO antiemetic guidelines have recommended the use of a NK-1 receptor antagonist, a 5-HT<sub>3</sub> receptor antagonist, and dexamethasone as the preferred prophylaxis for patients receiving high-dose, multi-day chemotherapy prior to autologous or allogeneic stem cell transplantation [20, 67]. The studies discussed above have demonstrated that the addition of aprepitant to a 5-HT<sub>3</sub> receptor antagonist and dexamethasone result in improved control of emesis post chemotherapy, but not nausea. The control of nausea remains a significant patient problem, not only in multi-day, high-dose chemotherapy, but also in single day highly emetogenic chemotherapy. Neither 5-HT<sub>3</sub> receptor antagonists, nor aprepitant appear to be effective anti-nausea agents in the post chemotherapy period [3, 6, 16, 17].

### 46.2.7.3 Cinvanti

Cinvanti is a substance P/neurokinin-1 (NK-1) receptor antagonist, approved by the FDA on November 9, 2017, indicated in adults, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin and nausea and vomiting associated with initial and repeat courses of MEC.

Cinvanti is a polysorbate 80-free, intravenous formulation of the NK<sub>1</sub> receptor antagonist fosaprepitant indicated for the prevention of acute and delayed CINV. Cinvanti does not contain polysorbate 80 or any other synthetic surfactant. Pharmaceutical formulations containing polysorbate 80 have been linked to hypersensitivity reactions, including anaphylaxis and irritation of blood vessels resulting in infusion-site pain [68]. Cinvanti was approved based on data demonstrating the bioequivalence of Cinvanti to fosaprepitant supporting its efficacy for the preven-

tion of acute and delayed CINV following HEC and MEC. Results from two pivotal randomized, crossover bioequivalence studies of Cinvanti and fosaprepitant IV showed subjects receiving Cinvanti reported fewer adverse events than those receiving fosaprepitant, including substantially fewer infusion-site reactions [68].

#### 46.2.7.4 Netupitant/NEPA

Netupitant is a NK-1 receptor antagonist approved by the FDA in 2014 for the prevention of chemotherapy-induced nausea and vomiting. *In vitro* and *in vivo* pharmacologic characterization demonstrated that Netupitant inhibits substance P in NK-1 receptors but was inactive for NK-2 and NK-3 receptors. This was demonstrated with intrathecal injections in mice, and intraperitoneally in both mice and gerbils. In all assays, aprepitant exhibited similar effects [69].

Netupitant behaves as a brain penetrant, is orally active, and is a potent and selective NK-1 antagonist [69, 70]. Rossi et al. [69] and Spinelli et al. [70] reported that positive emission tomography results demonstrate that netupitant is a potent agent targeting NK-1 receptors. It appears to have a high degree of occupancy (90%) for a long duration (96 h) when given as a single oral dose and appears to be well tolerated [69–71]. Netupitant has a high binding affinity, and a long half-life of 90 h compared to a 9–13 h half-life of aprepitant [8, 9, 69–71]. It is metabolized by CYP3A4 and is a moderate inhibitor of CYP3A4 [9, 69–71]. Due to netupitant's interaction with CYP3A4, it potentially could increase the concentration of docetaxel when administered simultaneously. However, netupitant would be expected to have similar interactions as aprepitant which has been shown not to cause any clinically significant alterations in the pharmacokinetics of docetaxel or of its toxicity (adverse events and neutropenia) compared with administration of docetaxel alone in cancer patients [59].

NEPA is an oral fixed-dose combination of netupitant and palonosetron which has been employed in phase II and phase III clinical trials for the prevention of CINV in patients receiving the chemotherapy combination of an anthracycline and cyclophosphamide and HEC [9, 72–74]. The clinical trials demonstrated that NEPA (300 mg of netupitant plus 0.50 mg of palonosetron) plus dexamethasone significantly improved the prevention of CINV compared to the use of palonosetron and dexamethasone alone in patients receiving either HEC [72] or a combination of an anthracycline and cyclophosphamide [73]. The significant improvement in the delayed period (24–120 h) and the overall period (0–120 h) post chemotherapy was maintained over multiple cycles of chemotherapy [74]. Adverse events (hiccups, headache, constipation) were few in number ( $\leq 3.5\%$ ) and were mild to moderate in severity [9, 72–74]. No cardiac adverse events were noted.

On October 10, 2014, oral NEPA (Akynzeo) was approved by the US FDA to treat nausea and vomiting in patients undergoing cancer chemotherapy [75].

### 46.2.7.5 Rolapitant

Rolapitant is a high affinity, highly-selective NK-1 receptor antagonist [76] It penetrates the central nervous system following oral administration, and it has a high affinity for the human NK-1 receptor and is highly selective over the human NK-2 and NK-3 receptor subtypes. It is a functionally competitive antagonist and reversed NK-1 agonist-induced foot tapping in a gerbil animal model following both intravenous and oral intravenous and oral administration [76]. Rolapitant reverses both apomorphine and cisplatin-induced emesis in ferrets [76].

The pharmacokinetics of rolapitant demonstrates that it has a long half-life (approximately 180 h) with high affinity ( $K_i = 0.66$  nM) for the NK-1 receptor [76, 77], and it does not induce or inhibit CYP3A4. Poma et al. [77] reported that rolapitant and its major metabolite SCH720 881 do not affect the pharmacokinetics of midazolam, a sensitive cytochrome P450 3A4 substrate. Rolapitant does not induce CYP3A4, and single oral doses of rolapitant, co-administered with midazolam were safe and well tolerated. Administration of rolapitant, unlike other NK-1 receptor antagonists aprepitant and netupitant, does not require dose adjustment of concomitantly administered drugs metabolized by CYP3A4.

Rolapitant is a moderate CYP2D6 inhibitor suggesting that there could be potential interactions with metoprolol or venlafaxine.

A phase I clinical trial in 14 healthy volunteers demonstrated that a 180 mg rolapitant dose provided  $\geq 90\%$  NK-1 receptor occupancy in the brain for up to 5 days following a single dose [10, 78]. A phase II randomized, double-blind, active-controlled dose-finding study showed that a 180 mg dose of rolapitant plus granisetron and dexamethasone was safe and effective in the prevention of CINV in patients receiving HEC [10, 79]. Complete response was significantly improved with rolapitant compared to placebo with all patients receiving ondansetron and dexamethasone.

The 180 mg dose of rolapitant was used in three large phase III clinical trials which demonstrated that rolapitant, granisetron, and dexamethasone significantly improved complete response compared to granisetron and dexamethasone alone in patients receiving MEC and HEC [10, 80, 81]. Approximately 80% of the patients in the MEC study [80] received a combination of an anthracycline and cyclophosphamide chemotherapy or carboplatin chemotherapy. There were no serious adverse events in the clinical trials, and there were no differences in the number of adverse events in the rolapitant or control arms.

On September 2, 2015, the US FDA approved oral Rolapitant (Varubi) for the prevention of nausea and vomiting associated with cancer chemotherapy. On October 25, 2017, the FDA approved an intravenous form of rolapitant equivalent to the oral form. Intravenous rolapitant is an emulsion, which is polysorbate 80 free.

**Table 46.12** Safety and tolerability of NK-1 receptor antagonists

Agent	Chemotherapy	No. of Patients	Adverse Events	References
Rolapitant	HEC	1070	Dyspepsia, headache	[81]
			Constipation, hiccups (not different from control)	
	MEC	1344	Constipation, fatigue,	[80]
			Headache, fatigue (not different from control)	
Netupitant	HEC	694	Hiccups, headache (not different from control)	[72]
	MEC	1455	Headache, constipation (not different from control)	[73]
Aprepitant	HEC	521	Asthenia, fatigue (not different from control)	[8]
Fosaprepitant	HEC	98	Phlebitis	[56]
	None	200	Infusion site reactions	[68]

### 46.2.8 Safety and Tolerability of Neurokinin-1 Receptor Antagonists

A ten-year review of the safety and efficacy of aprepitant and fosaprepitant [8] demonstrated that these agents are well tolerated, and there appear to be no major systemic adverse events associated with their use. In comparison studies, aprepitant treated patients have had patterns and incidences of adverse events similar to those associated with standard control antiemetic therapy [8] (Table 46.12). Both standard 3-day dosing of aprepitant and single-dose fosaprepitant have been demonstrated to be well tolerated after ondansetron and dexamethasone in patients receiving cisplatin [55]. The tolerability profiles of the two regimens appear similar, except for a higher incidence of infusion-site adverse events and significantly more phlebitis with intravenous fosaprepitant [56]. Higher incidence of infusion-site adverse events was observed in a retrospective review of 98 patients treated with fosaprepitant [56] and in randomized, cross-over bioequivalence studies of cinvanti and fosaprepitant in normal volunteers [68].

The recent studies on rolapitant and netupitant have also demonstrated a low level of adverse events, not different from comparison control antiemetic therapy, in patients receiving either MEC or HEC [72, 73, 80, 81] (Table 46.12). Headache, constipation, hiccups, and fatigue appear to be the most commonly reported events.

dos Santos et al. [82] reported that in a retrospective review of sixteen studies of the NK-1 receptor antagonists, the incidence of severe infection increased from 2% to 6% in the NK-1 receptor antagonist group in three RCTs with a total of 1480 patients. The increased infection rate was not seen in the other thirteen studies and was not reported in a ten-year review of aprepitant [8] or the recent phase III clinical trials of netupitant [72, 73] or rolapitant [80, 81]. A recent meta-analysis by Zhang

et al. [83] reported that NK-1 receptor antagonist-based triple regimens were effective in the prevention of chemotherapy-induced nausea and vomiting with few significant toxicities.

#### 46.2.8.1 Dexamethasone

Dexamethasone has been an effective antiemetic in controlling both acute and delayed CINV when combined with 5-HT<sub>3</sub> receptor antagonists and NK-1 receptor antagonists and it is essentially the main corticosteroid used as an antiemetic [19–21]. Dexamethasone added to a 5-HT<sub>3</sub> receptor antagonist improves the control of acute CINV, and it has been used as a single agent or in combination with NK-1 receptor antagonists in an attempt to control delayed CINV [19–21].

Concern has been expressed with the potential toxicity of the use of multiple-day dexamethasone to control CINV [84]. Patients receiving dexamethasone as prophylaxis for CINV reported moderate to severe problems with insomnia, hyperglycemia, indigestion, epigastric discomfort, agitation, increased appetite, weight gain and acne [84]. Some studies have demonstrated that dexamethasone use might be decreased from multiple days to 1 day in an antiemetic regime when used with other agents which are effective in controlling CINV in both the acute and the delayed periods [13, 21, 85, 86].

Celio et al. [85] used palonosetron in combination with a 1 day versus 3 days of dexamethasone to prevent CINV in patients receiving MEC. There was no improvement in complete response or no nausea over the 5-day overall period with the use of 3 days of dexamethasone versus 1 day of dexamethasone. A similar study [86] using palonosetron plus dexamethasone for 1 day versus 3 days for breast cancer patients receiving an anthracycline and cyclophosphamide chemotherapy showed similar results: no improvement in complete response or in no nausea over the 5-day overall period with the use of 3 days versus 1 day of dexamethasone.

Navari et al. [13, 21] reported that 4 days of olanzapine with 1 day of a 5-HT<sub>3</sub> receptor antagonist and 1 day of dexamethasone was effective in the prevention of CINV in patients receiving HEC.

#### 46.2.8.2 Olanzapine

Olanzapine is an atypical antipsychotic agent of the thienobenzodiazepine class and was approved by the FDA for the treatment of the manifestations of psychotic disorders in 1996 [87, 88] with a generic formulation becoming available in 2011. This drug blocks multiple neurotransmitter receptors including dopaminergic (D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub> brain receptors), serotonergic (5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub> receptors), catecholaminergic (alpha<sub>1</sub> adrenergic receptors), acetylcholinergic (muscarinic receptors), and histaminergic (H<sub>1</sub> receptors) [89]. Olanzapine has five times the affinity for 5-HT<sub>2</sub> receptors than for D<sub>2</sub> receptors [90]. The effect of olanzapine on the

serotonin-mediated 5-HT<sub>2C</sub> receptor as well as other dopamine and serotonin receptors may explain, in part, its efficacy in alleviating nausea and vomiting.

A benefit of olanzapine is that it is not a cytochrome P450 inhibitor and thus appears to have fewer drug interactions than many other drugs [89, 90]. Common side effects are sedation and weight gain [91]. The sedation is short term and may be dose dependent [92]. The weight gain can occur after higher doses given over a period of months and can lead to diabetes mellitus when given for a period of greater than 6 months [93].

Phase III clinical trials have demonstrated the effectiveness of olanzapine in the prevention of CINV [12–15, 94]. Olanzapine improved the control of nausea and emesis when added to azasetron and dexamethasone compared to azasetron and dexamethasone alone in patients receiving MEC and HEC [12]. Olanzapine, palonosetron, and dexamethasone improved the control of nausea compared to aprepitant, palonosetron, and dexamethasone in patients receiving HEC [13]. This antiemetic regimen has been recommended by the NCCN guidelines as an option for the prevention of CINV in patients receiving HEC [21].

The National Cancer Institute recently approved a multi-institutional phase III clinical trial (Alliance A221301) for the prevention of CINV in patients receiving highly emetogenic chemotherapy using olanzapine plus standard antiemetics compared to placebo plus standard antiemetics [14]. The trial was based on substantial evidence that this drug is helpful for preventing chemotherapy-induced nausea and vomiting [11–13] and for treating nausea/vomiting that had occurred as a result of chemotherapy [47]. This randomized, double blind, phase III trial was performed in chemotherapy naïve patients receiving cisplatin,  $\geq 70$  mg/m<sup>2</sup>, or cyclophosphamide-anthracycline-based chemotherapy, comparing olanzapine (OLN) to placebo (PLA) in combination with aprepitant (APR), a 5-HT<sub>3</sub> receptor antagonist (5-HT<sub>3</sub>), and dexamethasone (DEX). The OLN regimen was 10 mg of oral OLN, 125 mg oral APR, a 5-HT<sub>3</sub>, and oral DEX 12 mg pre-chemotherapy, day 1, and 10 mg/day of oral OLN on days 2–4 post-chemotherapy, 80 mg oral APR, days 2, 3 post chemotherapy, and 8 mg oral DEX, days 2–4 post chemotherapy. The PLA regimen was oral placebo, day 1, and oral placebo on days 2–4 post chemotherapy, with the APR, 5-HT<sub>3</sub>, and DEX pre and post-chemotherapy being the same as in the OLN regimen. Fosaprepitant (150 mg IV), day 1 could be substituted for the oral aprepitant. Palonosetron, ondansetron, or granisetron were the permitted 5-HT<sub>3</sub> options. Nausea was measured on a 0–10 visual analogue scale, with 0 being no nausea at all and 10 being nausea as bad as it can be.

Four hundred one patients were enrolled with 380 patients evaluable (192 patients receiving the OLN regimen and 188 patients receiving the PLA regimen). The proportion of patients with no nausea was significantly improved for the OLN regimen compared to the PLA regimen for the acute period (24 h post-chemotherapy) (74% vs. 45%,  $p = 0.002$ ), for the delayed period (25–120 h post-chemotherapy) (42% vs. 25%,  $p = 0.002$ ), and for the overall period (0–120 h) (37% vs. 22%,  $p = 0.002$ ). Complete response (CR) (no emesis, no rescue medications) was significantly improved in OLN compared to PLA patients for the acute (86% vs. 65%,  $p < 0.001$ ), the delayed (67% vs. 52%,  $p = 0.007$ ), and the overall periods (64% vs.

41%,  $p < 0.001$ ). There were no Grade 3 or 4 toxicities. No nausea, the primary endpoint, and complete response, a secondary endpoint, were significantly improved with OLN compared to PLA [14]. Based on the results of this study [14], the NCCN, ASCO, and MASCC/ESMO antiemetic guidelines have recommended the use of olanzapine, a 5-HT<sub>3</sub> receptor antagonist, a NK-1 receptor antagonist, and dexamethasone as the preferred prophylaxis for the prevention of CINV in patients receiving HEC [19–21].

A recent study has compared olanzapine to metoclopramide for the treatment of breakthrough emesis and nausea in patients receiving HEC and guideline-directed antiemetic prophylaxis. Olanzapine was significantly better than metoclopramide for the treatment of breakthrough emesis and nausea. This was the first phase III study on the treatment of breakthrough emesis and nausea [47]. Based on this study [47], olanzapine has been recommended for use for the treatment of breakthrough chemotherapy-induced nausea and vomiting by both the NCCN antiemetic guidelines [21] and ASCO antiemetic guidelines [20].

### 46.2.8.3 Gabapentin

Gabapentin is a gamma aminobutyric acid (GABA) analogue that has been used for the treatment of seizures, chronic neuropathic pain, CINV, and post-herpetic neuralgia [95, 96]. The mechanism of action exerted by gabapentin is unknown. Gabapentin is structurally related to the neurotransmitter GABA, but it does not interact with GABA receptors, is not converted metabolically into GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation [96].

Guttuso et al. [97] reported an improvement in CINV in six of nine breast cancer patients when gabapentin was used to prevent nausea. Cruz et al. [98] added gabapentin to ondansetron, dexamethasone and ranitidine to prevent CINV in patients receiving HEC. The complete response was significantly improved in the patients receiving gabapentin but nausea was not significantly improved (no nausea, overall: 62% vs. 45%).

A phase III double-blind, placebo-controlled study of gabapentin for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy has been reported. All patients received a 5-HT<sub>3</sub> receptor antagonist and dexamethasone prior to chemotherapy and dexamethasone post chemotherapy. Patients were randomized to 5 days of gabapentin or placebo starting with the day of chemotherapy. In this study, gabapentin did not significantly improve delayed CINV [99].

### 46.2.8.4 Cannabinoids

Studies in animal models have suggested that delta-9-tetrahydrocannabinoid (dronabinol) selectively acts on CB1 receptors in specific regions of the dorsal vagal complex to inhibit emesis [100, 101]. A few reported studies have explored this



mechanism in patients [102, 103]. Meiri et al. [102] looked at the efficacy of dronabinol versus ondansetron in patients receiving chemotherapy for a wide variety of neoplasms. Dronabinol and ondansetron were similarly effective antiemetic treatments in 61 patients receiving MEC and HEC.

Nabilone is a synthetic cannabinoid, a racemic mixture of isomers, that mimics the main ingredient of cannabis (dronabinol). A recent review of the published English literature on the use of oral nabilone in the treatment of CINV concluded that cannabinoids do not add to benefits of the 5-HT<sub>3</sub> receptor antagonists [103].

At this time, there is insufficient data to support the routine use of dronabinol or nabilone [103–105] as preventative antiemetics in all chemotherapeutic regimens. Limited data suggest that dronabinol may be effective for some patients in the breakthrough CINV setting [20, 104, 105]. Further study of the scope of cannabinoid's potential efficacy is warranted.

#### 46.2.8.5 Ginger

Ginger is an herbal supplement that has been used for reducing the severity of motion sickness, pregnancy-induced nausea and post-operative nausea and vomiting [106]. The mechanism of action by which ginger might exert antiemetic effects is unclear. Animal studies have described enhanced GI transport, anti-5-hydroxytryptamine activity and possible central nervous system antiemetic effects. Human experiments to determine the mechanism of action show varying results regarding gastric motility and corpus motor response [106].

Pillai et al. [106] added ginger to ondansetron and dexamethasone in children and young adults receiving HEC and reported a reduction in the severity of acute and delayed CINV, but all patients had some nausea in days 1–4 post-chemotherapy. Zick et al. [107] reported that ginger provided no additional benefit for reduction of the prevalence or severity of acute or delayed CINV when given with 5-HT<sub>3</sub> receptor antagonists and/or aprepitant in 162 cancer patients receiving chemotherapy. Ryan et al. [108] gave ginger before and after chemotherapy administration to 644 patients receiving a wide variety of chemotherapy regimens and found a reduction in nausea during the first day of chemotherapy.

At present, the available studies do not support ginger as an agent to recommend for the prevention of CINV. There are ongoing studies to determine if there is a role for ginger in the prevention of chemotherapy-induced nausea and vomiting [109].

## 46.3 Clinical Management of CINV

### 46.3.1 Principles in the Management of CINV

International antiemetic guidelines [19–21] form the basis for the recommendations for the management of CINV. As new information and new studies emerge, these guidelines will evolve to provide the highest quality evidence-based clinical practice.

#### 46.3.1.1 Single-Day Chemotherapy (Table 46.13)

For patients receiving **HEC**, current evidence suggests the following [19–21].

- Pre-chemotherapy—olanzapine with any of the 5-HT<sub>3</sub> receptor antagonists, plus an NK-1 receptor antagonist plus dexamethasone The guidelines suggest that the

**Table 46.13** International Antiemetic Guidelines for Chemotherapy Induced Nausea and Vomiting

### Guidelines for high emetic risk

	Acute CINV	Delayed CINV (D 2-4)
NCCN	5-HT <sub>3</sub> RA + Dex + NK-1 RA <sup>a</sup>	Dex ± Aprepitant
	Netupitant/Palonosetron (300 mg/0.5 mg) + Dex	Dex
	Olanzapine + Palonosetron + Dex	Olanzapine
	5-HT <sub>3</sub> RA + Aprepitant + Dex + Olanzapine	Olanzapine + Dex ± Aprepitant
ASCO	Olanzapine + 5-HT <sub>3</sub> RA + Dex + NK-1 RA	Olanzapine + Dex ± Aprepitant
MASCC	Olanzapine + 5-HT <sub>3</sub> RA + Dex + NK-1 RA	Dex ± Aprepitant

Examples include cisplatin in combination with cyclophosphamide for the treatment of metastatic ovarian cancer and the combination of doxorubicin and cyclophosphamide for the treatment of metastatic breast cancer

Recommendations for HEC are similar across guidelines (NCCN 2017; Basch et al. 2011; Roila et al. 2016)

(continued)

**Table 46.13** (continued)

## Guidelines for moderate emetic risk

	Acute CINV	Delayed CINV (D 2-3)
NCCN	5-HT <sub>3</sub> RA (Palonosetron or granisetron SQ preferred) + Dex (category 1) ± NK-1 RA	Dex ± Aprepitant
	Netupitant/Palonosetron (300 mg/0.5 mg) + Dex	Dex
	Olanzapine + Palonosetron + Dex	Olanzapine
ASCO	5-HT <sub>3</sub> RA (palonosetron preferred) + Dex	Dex
MASCC	Palonosetron + Dex	Dex

Examples include irinotecan in combination with 5-fluorouracil/leucovorin for the treatment of metastatic colorectal cancer and oxaliplatin in combination with 5-fluorouracil/leucovorin for the treatment of advanced colorectal cancer

For acute CINV, the base recommendation is 2-drug regimens

Final treatment decisions are based on patient factors and physician’s choice

For delayed CINV, there is slightly more variation (NCCN 2017; Basch et al. 2011; Roila et al. 2016)

## Guidelines for low and minimal emetic risk

	Low emetic risk	Minimal emetic risk
NCCN	5-HT <sub>3</sub> RA OR Dex OR Metoclopramide OR Prochlorperazine	No routine prophylaxis
ASCO	Dex	No routine prophylaxis
MASCC	5-HT <sub>3</sub> RA OR Dex OR Dopamine RA	No routine prophylaxis

Examples include docetaxel for the treatment of non-small cell lung cancer after platinum therapy failure and gemcitabine for the treatment of pancreatic cancer

Dex dexamethasone, SQ subcutaneous

<sup>a</sup>Aprepitant or fosaprepitant

combination of cyclophosphamide and doxorubicin should be considered as HEC and the appropriate preventative agents should be used.

- Post-chemotherapy—olanzapine with or without dexamethasone or dexamethasone alone.

For patients receiving **MEC**, current evidence suggests the following [19–21].

- Pre-chemotherapy—the 5-HT<sub>3</sub> receptor antagonist palonosetron plus dexamethasone. If palonosetron is not available, ondansetron or granisetron may be employed.
- Post-chemotherapy—dexamethasone on days 2–4.

Antiemetic guidelines of the past have included the available oral first-generation 5-HT<sub>3</sub> receptor antagonists as optional therapy for the prevention of delayed emesis, but the level of evidence supporting this practice is low [34, 110]. The first-generation 5-HT<sub>3</sub> receptor antagonists are no longer recommended for use post-chemotherapy [19–21].

For patients receiving low emetogenic chemotherapy, a single agent in the form of a 5-HT<sub>3</sub> receptor antagonist, dexamethasone, or a phenothiazine, depending on the clinical situation, should be used pre-chemotherapy, and an antiemetic following chemotherapy should be given only as needed.

#### 46.3.1.2 Treatment of Breakthrough CINV

Phenothiazine, metoclopramide, dexamethasone or olanzapine may be effective in the treatment of breakthrough nausea and vomiting [21]. A 5-HT<sub>3</sub> receptor antagonist may also be effective unless a patient presents with nausea and vomiting that developed following the use of a 5-HT<sub>3</sub> receptor antagonist as prophylaxis for chemotherapy or radiotherapy-induced emesis. It is very unlikely that breakthrough nausea and vomiting will respond to an agent in the same drug class after unsuccessful prophylaxis with an agent with the same mechanism of action.

Patients who develop nausea or vomiting post-chemotherapy (days 1–5) despite adequate prophylaxis should be considered for treatment with a regimen of 3 days of oral or sublingual olanzapine or oral metoclopramide. A recently completed phase III study demonstrated that oral olanzapine (10 mg/day for 3 days) was significantly better than oral metoclopramide (10 mg three times daily for 3 days) in controlling both emesis and nausea in patients receiving HEC who developed breakthrough CINV despite guideline-directed prophylactic antiemetics [20, 47].

It is important to note that aprepitant has been approved as an additive agent to a 5-HT<sub>3</sub> receptor antagonist and dexamethasone for the prevention of CINV. It has not been studied and should not be used to treat breakthrough nausea and vomiting.

### 46.3.1.3 Refractory CINV

Patients who develop CINV during subsequent cycles of chemotherapy when antiemetic prophylaxis has not been successful in controlling CINV in earlier cycles should be considered for a change in the prophylactic antiemetic regimen. If anxiety is considered to be a major patient factor in the CINV, a benzodiazepine such as lorazepam or aprazolam can be added to the prophylactic regimen. If the patient is receiving HEC, olanzapine (days 1–4) may be added to a prophylactic regimen of a 5-HT<sub>3</sub> receptor antagonist, a NK-1 receptor antagonist, and dexamethasone [14, 19–21] or substituted for a NK-1 receptor antagonist in combination with a 5-HT<sub>3</sub> receptor antagonists and dexamethasone [13, 21]. If the patient is receiving MEC, an NK-1 receptor antagonist may be added to a palonosetron and dexamethasone antiemetic regimen [21].

### 46.3.1.4 Anticipatory CINV

In order to prevent the occurrence of anticipatory CINV, patients should be counseled prior to the initial course of treatment concerning their ‘expectations’ of CINV. Patients should be informed that very effective prophylactic antiemetic regimens will be used and that 70–75% of patients will have a complete response (no emesis, no use of rescue medications). Patients risk factors for CINV should be carefully evaluated, and the most effective prophylactic antiemetic regimen for the patient’s specific type of chemotherapy should be used prior to the first course of chemotherapy in order to obtain the optimum control of CINV during the first course of chemotherapy. If CINV is effectively controlled during the first chemotherapy cycle, it is likely that the patient will have effective control during subsequent cycles of the same chemotherapy. If the patient has a poor experience with CINV in the first cycle, it may be more difficult to control CINV in subsequent chemotherapy cycles, and refractory and/or anticipatory CINV may occur. The use of anti-anxiety medications such as lorazepam or another benzodiazepine may be considered for excess anxiety prior to the first course of chemotherapy in order to obtain an optimum outcome and prevent anticipatory CINV. If anticipatory CINV occurs despite the use of prophylactic antiemetics, behavioural therapy might be considered [111, 112].

### 46.3.1.5 Multi-Day Chemotherapy and High-Dose Chemotherapy with Stem Cell or Bone Marrow Transplantation

The success of the use of NK-1 receptor antagonists with 5-HT<sub>3</sub> receptor antagonists and dexamethasone in preventing emesis in patients receiving single day highly emetogenic chemotherapy [3, 6] prompted the use of the NK-1 receptor antagonist aprepitant combined with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone in patients receiving multi-day, high dose chemotherapy prior to SCT. A number of Phase II

and III studies have been reported with the use of the NK-1 aprepitant added to a 5-HT<sub>3</sub> receptor antagonists and dexamethasone [60–66] in patients receiving multi-day, high dose chemotherapy prior to autologous or allogeneic stem cell transplant (SCT). As a result of these studies, the 2017 ASCO and the 2017 MASCC/ESMO antiemetic guidelines have recommended the use of a NK-1 receptor antagonist, a 5-HT<sub>3</sub> receptor antagonist, and dexamethasone as the preferred prophylaxis for patients receiving high-dose, multi-day chemotherapy prior to autologous or allogeneic stem cell transplantation [20, 67]. The recent studies [60–66] have demonstrated that the addition of aprepitant to a 5-HT<sub>3</sub> receptor antagonist and dexamethasone resulted in improved control of emesis post chemotherapy, but not nausea. The control of nausea remains a significant patient problem, not only in multi-day, high-dose chemotherapy, but also in single day highly emetogenic chemotherapy. Neither 5-HT<sub>3</sub> receptor antagonists, nor the NK-1 receptor antagonists appear to be effective anti-nausea agents in the post chemotherapy period [3, 6, 14, 16].

#### 46.4 Prevention and Treatment of Nausea

The current data in the literature from multiple large studies suggest that the first or second-generation 5-HT<sub>3</sub> receptor antagonists and the NK-1 receptor antagonists have not been effective in the control of nausea in patients receiving either MEC or HEC, despite the marked improvement in the control of emesis with these agents [16–18]. It appears that neither the serotonin nor the substance P receptors may be important in mediating nausea. Phase III studies with olanzapine have demonstrated very good control of both emesis and nausea in patients receiving either MEC or HEC [12–14]. Preliminary small studies with gabapentin, cannabinoids and ginger are inconclusive in defining their role, if any, in the prevention of nausea. At this time, olanzapine appears to have high potential for the prevention of both emesis and nausea in patients receiving MEC or HEC [12–14]. If patients are having difficulty with significant nausea, consideration should be given to including olanzapine in their prophylactic antiemetic regimen [12–14]. Olanzapine may also be efficacious in the treatment of breakthrough nausea [47].

#### 46.5 Conclusions and Future Directions

The introduction of the 5-HT<sub>3</sub> receptor antagonists combined with the use of dexamethasone significantly improved the prevention of acute emesis in patients receiving MEC or HEC. The 5-HT<sub>3</sub> receptor antagonists have been safe and well tolerated with a minority of patients experiencing a mild headache, mild diarrhea, or mild constipation. There have been concerns with the potential of the prolongation of the QT interval with the use of the 5-HT<sub>3</sub> receptor antagonists. These concerns have resulted in the FDA recommendations of discontinuing the use of dolasetron for the

prevention of CINV and a restriction of the higher intravenous doses of ondansetron. Granisetron and palonosetron appear to have much less potential for prolongation of the QT interval with no restrictions by the FDA on their use. The prevention of chemotherapy-induced nausea and emesis in the delayed period have not been effective with the use of the first generation 5-HT<sub>3</sub> receptor antagonists, and they are no longer recommended for use as prophylaxis in the delayed period. The second generation 5-HT<sub>3</sub> receptor antagonist palonosetron may be more effective in the prevention of nausea and emesis in the delayed period.

Dexamethasone has improved the control of CINV in the acute and delayed periods when used in combination with other antiemetics. Patients have experienced insomnia and varying degrees of gastric irritability with the use of dexamethasone. Some studies have demonstrated effective prevention of CINV in patients receiving MEC or the combination of an anthracycline and cyclophosphamide chemotherapy with the use of palonosetron plus 1 day versus 3 days of dexamethasone. In addition, studies have demonstrated that olanzapine, palonosetron, and 1 day of dexamethasone may be effective in the prevention of CINV in patients receiving HEC.

The use of the NK-1 receptor antagonists in combination the 5-HT<sub>3</sub> receptor antagonists and dexamethasone has significantly improved the control of emesis in the acute and delayed phase in patients receiving HEC. Aprepitant, fosaprepitant, netupitant, and rolapitant have been shown to be safe and effective in phase III clinical trials with few adverse events. Aprepitant, fosaprepitant, and netupitant are metabolized by the liver enzyme CYP3A4 and are moderate inhibitors of CYP3A4, potentially resulting in drug interactions. There have been few, if any, clinical adverse events attributable to CYP3A interactions with these NK-1 receptor antagonists. Rolapitant does not induce CYP3A4.

Olanzapine, a US FDA approved antipsychotic, has been shown to be safe and effective in preventing both nausea and emesis in patients receiving MEC or HEC. With the exception of mild sedation, which appears to be well tolerated, there have been no reported adverse events associated with the use of olanzapine on the day of chemotherapy or days 2–4 post chemotherapy. Olanzapine also appears to be an effective agent in the treatment of breakthrough emesis and nausea.

Recent phase III studies have demonstrated that the addition of aprepitant to a 5-HT<sub>3</sub> receptor antagonist and dexamethasone has improved the control on emesis in patients received high dose, multi-day chemotherapy prior to stem cell transplant. The recent updated antiemetic guidelines have recommended the use of this three drug regimen for high dose, multi-day chemotherapy.

Oncology practitioners currently have very effective antiemetic agents for the prevention of CINV in patients receiving MEC or HEC. The choice of individual agents and the combination of agents should be dictated by the emetogenicity of the chemotherapy that is to be administered and patient risk factors. Antiemetic choices should be guided by the international antiemetic guidelines. The available agents for the prevention of CINV appear to be safe and effective with few reported adverse events.

The first generation 5-HT<sub>3</sub> receptor antagonists ondansetron and granisetron have similar efficacy and compete only on an economic basis. Both are available as

generics. The second generation 5-HT<sub>3</sub> receptor antagonist palonosetron is the recommended 5-HT<sub>3</sub> receptor antagonist by some of the international guidelines; it is not yet available in generic form. When used in the recommended doses, these agents should be safe with few adverse events.

Dexamethasone should be used in conjunction with the 5-HT<sub>3</sub> receptor antagonists, and consideration should be given to using it on the day of chemotherapy only in conjunction with other effective antiemetics to minimize any adverse events.

At present, there is only one definitive published clinical trial reporting a direct comparison of the efficacy and safety of the various NK-1 receptor antagonists (aprepitant, fosaprepitant, cinvanti, netupitant, rolapitant). Zhang et al. reported a phase III randomized, double-blind clinical trial in patients receiving cisplatin-based chemotherapy [113] in which 828 patients were randomized to receive NEPA plus dexamethasone or aprepitant, granisetron and dexamethasone. The primary endpoint of complete response (no emesis, no rescue) demonstrated that there was no difference in the two regimens, both of which were well tolerated.

There are some pharmacokinetic differences between rolapitant and the other commercially available, oral NK-1 receptor antagonists. Rolapitant has a longer half-life (180 h) than aprepitant (9–13 h) and netupitant (90 h) which may be important in multiple-day chemotherapy clinical settings. Future studies may determine if this may be an important clinical issue.

Rolapitant does not induce or inhibit CYP3A4, unlike the other NK-1 receptor antagonists, aprepitant and netupitant. Among the class of NK-1 receptor antagonists, this unique feature corresponds to a reduced propensity of drug interactions that may decrease the need for dose modifications of other drugs metabolized by CYP3A4 when administered concomitantly with rolapitant. A rolapitant antiemetic regimen may simplify medical management of some oncology patients, who may be receiving multiple medications.

Based on the available clinical trial data, the NK-1 receptor antagonists have significantly improved the prevention of acute and delayed emesis in patients receiving HEC and have few adverse events. There is little evidence, however, that these agents are effective in controlling nausea. Although there appear to be other NK-1 receptor antagonists in development, there does not appear to be any which are pending regulatory approval in the near future.

Olanzapine appears to be an effective agent in the control of emesis and nausea when combined with other antiemetic agents. At present, olanzapine appears to be the only current effective agent for the control of nausea. Nausea appears to be an important and prevalent clinical issue, despite the control of emesis with the 5-HT<sub>3</sub> receptor antagonists, dexamethasone, and the NK-1 receptor antagonists. When used for a period of 4 days (pre- and post- chemotherapy), olanzapine is associated with only mild sedation.

The current antiemetics that are recommended by the various international antiemetic guidelines are safe and effective in the prevention of chemotherapy-induced nausea and vomiting when used in the recommended doses. These guidelines should be followed by practitioners in order to provide the highest possible quality of care for patients receiving chemotherapy.



## Clinical Cases

### Case Study 1:

- Patient is a 65-year-old man, former 2 pack/d smoker who quit 1 year ago. He sees his primary care physician for a cough that has lasted 4 weeks
- Chest X-ray reveals a poorly differentiated mass confined to the upper right lobe, and a CT/PET scan shows a tumor measuring  $4.5 \times 2.0$  cm and possible intrapulmonary lymph node involvement, with no evidence of distant metastasis
- Surgical resection with mediastinal lymph node dissection is performed. Pathology reveals stage II adenocarcinoma
- After discussion of adjuvant chemotherapy options with the treatment team, a regimen of paclitaxel and carboplatin is selected. Although a cisplatin regimen would be first choice for most patients at this stage, it is contraindicated in this patient because he has moderate bilateral hearing impairment
- Adjuvant therapy regimen:

Paclitaxel 200 mg/m<sup>2</sup> IV over 3 h

Carboplatin AUC 6 mg/mL/min IV over 45–60 min

Repeat every 21 days for 4 cycles

Which CINV prophylactic regimen would you recommend?

Palonosetron/dexamethasone

Netupitant/palonosetron/dexamethasone

Prochlorperazine

Metoclopramide

NK-1 RA + 5-HT<sub>3</sub> + Dex + Olanzapine

Is this chemotherapy regimen moderately or highly emetogenic chemotherapy?

### Case Study 2:

- 48-year-old mother of 3 diagnosed with invasive ductal carcinoma, HER2–/ER–/PR– tumor
- Underwent a lumpectomy and axillary dissection
- Histopathology revealed 3-cm primary tumor and involvement in 3 of 18 lymph nodes
- Agrees to a “dose-dense” doxorubicin/cyclophosphamide followed by paclitaxel and radiation therapy
- Risk factors for emesis include hyperemesis of pregnancy, low alcohol intake
- Receives ondansetron/aprepitant/dexamethasone for prophylaxis and dexamethasone for Days 2 and 3
- Develops nausea and vomiting (Breakthrough CINV) on Day 4 after chemotherapy

How would you treat the Breakthrough CINV?

IV fluids

Dexamethasone

Olanzapine

All of the above

How would you modify the patient's antiemetic regimen for the next chemotherapy cycle?

Add dolasetron

Add olanzapine

Add fosaprepitant

None of the above

### Case Study 3:

- 55-year-old woman with advanced colorectal cancer
- Social history: Former smoker, nondrinker
- Medical history: Currently receiving treatment for hypertension, dyslipidemia, and insomnia
- Chemotherapy regimen: FOLFOX + bevacizumab IV every 14 days
- Scheduled for second cycle of chemotherapy, but experienced nausea/vomiting several days after initiation of first cycle
- Antiemetic prophylaxis with ondansetron and dexamethasone

What is the best option to improve the patient's control of CINV in cycle 2 of FOLFOX?

Switch ondansetron to granisetron

Increase prochlorperazine dosing in the delayed phase

Add fosaprepitant to the prophylactic regimen

Administer olanzapine as a rescue medicine

Both c and d

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# Chapter 47

## Asthenia



F. Koinis and I. Gioulbasanis

**Abstract** In the era of holistic care, management of patients with malignant diseases should also embrace the effort for palliation of symptoms hampering the physical, mental and social well-being of the patient.

**Keywords** Asthenia · Palliative care · End of life

### 47.1 Introduction

In the era of holistic care, management of patients with malignant diseases should also embrace the effort for palliation of symptoms hampering the physical, mental and social well-being of the patient. Asthenia or cancer-related fatigue (CRF) is well acknowledged as one of the most common symptoms in cancer patients receiving anti-neoplastic therapy but also prevailing as a post-treatment remnant at the end of life, or even persisting for years in cancer survivors. It is often described as part of a symptom cluster, together with pain and depression [1]. It has been shown to have a major debilitating effect on patients' daily routine with indirect consequences on caregivers and family members as well. Apart from the physical impairment, asthenia has also mental and emotional dimensions interfering with patients' ability to perform activities of daily living and negatively affecting the social and economic status of the patients and their caregivers. The Fatigue-2 study demonstrated fatigue as the most prevalent symptom while receiving chemotherapy, with its impact on the patients' quality of life (QOL) enduring longer than the effects of pain or depression [2].

This chapter addresses the epidemiology and pathophysiology of asthenia and provides a thorough insight in the screening, evaluation and management of cancer patients reporting this symptom.

It must be noted that the terms 'asthenia' and 'CRF' are being used interchangeably throughout this manuscript.

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## 47.2 Definitions and Prevalence

Etymologically the word asthenia derives from the privative prefix a- and the Greek word “sthenos”, which means strength. Thus, asthenia is the lexical equivalent of weakness. Until recently, ‘asthenia’ referred to the subjective sensation of exhaustion while ‘fatigue’ delineated a symptom of effort-dependent devitalization. Nowadays the terms ‘asthenia’ and ‘fatigue’ are being used interchangeably in the medical literature, while the latter is adapted by the NCI-CTCAE [3] (Table 47.1). The National Comprehensive Cancer Network (NCCN) defines fatigue as a subjective state of physical, emotional and/or cognitive exhaustion which is not proportional to any recent change in activity level and that interferes with usual functioning [4]. Nevertheless, patients and healthcare professionals describe it using a variety of expressions [5]. Thus, patients often report weakness, tiredness, exhaustion or feeling slow and worn out, whereas physicians address asthenia as energy deficiency, exercise intolerance, malaise and prostration.

Although asthenia represents a frequent clinical occurrence among cancer patients, its actual prevalence remains to be defined. It is estimated that 4–99% of cancer patients experience asthenia during the course of their illness [6–8]. The wide range of this estimate could be attributed to the heterogeneity of the epidemiological studies (study population, asthenia definition, methods used to quantify fatigue) from which these data were derived.

In particular, asthenia rates are higher among patients receiving active treatment. Stashi R et al. reported that while 50–75% of patients presented at the time of diagnosis with asthenia, a higher rate experienced asthenia during chemotherapy (80–96%) or radiotherapy (60–93%) courses [9]. These rates remain high or even increase as patients with incurable disease progress [10]. Moreover, it seems that fatigue persists in a substantial proportion (~30%) of patients rendered disease-free after completion of therapy (chronic fatigue) [11]. Indeed, a higher prevalence of persistent asthenia is reported in women surviving breast cancer compared to individuals without a history of cancer [12, 13].

**Table 47.1** Grading of fatigue according to NCI-CTCAE v4.03

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
FATIGUE	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	—	—

*NCI-CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events, *ADL* activities of daily living

Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute. Available at: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) (Accessed March 15, 2015)

Lower rates of asthenia are reported from studies adopting more explicit diagnostic criteria. According to a validation study in cancer survivors, although 37% of patients reported fatigue, only 17% of them met the proposed ICD-10 criteria for the diagnosis of CRF [11]. Contrarily, studies using telephone interviews reported higher prevalence of asthenia among cancer patients [14, 15]. In these trials fatigue was “defined” as a positive answer to the question: “Do you feel tired?”

Taking into account its subjective nature, the unconformity between the reported rates of asthenia when patients, caregivers or oncologists are asked seems justifiable. Generally, caregivers report higher rates than patients. Although oncologists’ estimation of asthenia prevalence is even lower, they believe that this clinical syndrome is underdiagnosed [15].

Finally, patients with glioblastoma [16], lung cancer [17] and patients with bone metastases and compromised respiratory function due to extensive lung disease seem to exhibit a higher incidence of asthenia. The latter demonstrate the role of other symptoms (pain, dyspnea) in enhancing fatigue severity [10].

### 47.3 Pathophysiology

Beginning in the 1980’s, efforts have been mounted to shed light on asthenias’ pathophysiology. It is now believed to be multifactorial, as inflammatory cytokines dictate the synergistic interactions between treatment, host and tumor mechanisms. Studies in humans and animal models provide the theoretical background of the proposed hypotheses. Overall, two major components of CRF have been recognized: (i) a central, involving dysregulation of serotonin neural-signaling pathways, hypothalamic-pituitary-adrenal (HPA) axis impairment, vagal-afferent signaling, circadian rhythm dysregulation and (ii) a peripheral, related with altered muscle metabolism (decreased ATP concentration and protein synthesis, increased lactate production). Increased inflammatory activity, reflected by high – plasma and tumor tissue- levels of cytokines, relies on the core of the above mentioned processes.

Inflammation has been recognized as a fundamental process in oncogenesis and tumor progression [18–20]. There is a growing amount of evidence showing a strong correlation between high levels of several mediators and biomarkers of inflammation with asthenia, both in patients with various tumor types [17, 21–23], as well as in cancer survivors [24–26]. In this chronic inflammatory response, the T-cell immunity plays a fundamental role. Bower et al. have shown that breast cancer survivors reporting persistent fatigue had significantly elevated CD4+ and CD56+ T-cell subpopulation compared to non-fatigued survivors [27]. In mice models, tumor progression was associated with depressive-like behaviors and fatigue even before any loss of muscle mass was documented. These alterations came together with an increase in IL-1 $\beta$  expression in the cortex and hippocampus of the mice [28]. In humans, it has been proposed that peripheral inflammation, generated by cancer itself or antineoplastic treatment, leads to production of various cytokines [29]. Pro-inflammatory cytokines, then, cross the blood-brain barrier and

act on neural signaling of behavioral circuits in the central nervous system (CNS) that regulate emotion, cognition, motivation and vigilance [30]. The final result from the above described interaction is the emergence of certain symptoms that frequently co-occur [31]. These include asthenia, depression and sleep disturbances [32]. Specifically, IL-6 plasma levels have been positively correlated with fatigue, poor sleep quality and major depressive episodes in breast cancer and pancreatic cancer patients, respectively [33, 34]. Finally, it has been suggested that certain gene polymorphisms are associated with fatigue via regulation of pro-inflammatory cytokine production [35–38]. Nevertheless, these early findings require further validation in larger prospective trials [39].

In healthy individuals increased 5-HT levels [40] and up-regulation or increased sensitivity of 5HT-receptors in the hypothalamus [41] are associated with the development of fatigue after prolonged exercise. In cancer patients, cytokines such as TNF $\alpha$  or IL-1 are thought to enhance serotonergic signaling in the CNS, as has been shown in cell lines and animal models [42–44].

The HPA axis normally regulates cortisol production. Fatigue has been linked with down-regulated HPA axis function and hypocortisolemia [45]. It is believed that pro-inflammatory cytokines in the context of cancer may disrupt HPA axis function via diminishing corticotropin-release hormone stimulation [46, 47]. In a study, women with breast cancer experiencing fatigue had lower serum cortisol levels than non-fatigued patients [48, 49]. However, other studies report an inverse relation between cortisol –or its metabolites- levels and fatigue [50, 51]. Moreover, various medical disorders such as sleep disturbance [52] and treatment modalities -e.g. radiotherapy, specific chemotherapy agents and glyocorticoids [53–55]- may directly influence HPA axis function, contributing to the emergence of CRF. As a conclusion, the connection between HPA axis dysregulation and asthenia remains unclear.

Circadian rhythm dysregulation has been implicated in the development of asthenia through two different pathways: altered patterns of endocrine organ function and sleep disorders. Several studies have found frequent circadian rhythm disruption in cancer patients, conferring a poor prognosis by inducing tumor progression [56, 57]. In particular, Bower et al. has reported rather flattened diurnal cortisol slope in breast cancer patients experiencing fatigue [58], while Weinrib et al. showed a strong association between nocturnal cortisol dysregulation and fatigue in ovarian cancer patients [59]. It is proposed that in the context of the systemic inflammatory response in cancer patients, TGF $\alpha$  promotes fatigue by dismantling the circadian axis through interaction with the epidermal growth factor receptor [60, 61]. Furthermore, fatigue positively correlates with sleep disorders such as restless sleep [62–64]. Particularly, in breast cancer patients disrupted sleep patterns were associated with flattened circadian rhythms and fatigue, irrespective of the presence of depression [65].

According to the vagal-afferent-activation hypothesis, pro-inflammatory cytokines and factors released from tumor tissue may act as neuro-modulating agents, stimulating vagal-afferent nerves. This activation causes a reduction in motor-muscle functional capacity [49] and promotes “sickness-behaviors” (e.g. depres-

sion, sleep disorders, fatigue, psychomotor slowing, anorexia) [30]. Several studies in animal models have provided evidence of a vagal reflex resulting in certain behavioral changes that enhance the debilitating sense of asthenia [66–68], probably via vagal nerve-mediated IL-1 $\beta$  production [69, 70]. In support of the latter, it has recently been shown that vagotomy reduces non-rapid eye movement sleep (NREMS) by undermining the TNF $\alpha$ -induced IL-1 $\beta$  production in the brain of mice [71]. However, it should be noted that this theory remains to be confirmed in humans. There is only indirect proof for increased vagal nerve activity in fatigued cancer patients [72].

ATP is the energy currency of human cells and the main source of energy for skeletal muscles. Asthenia, also described as lack of energy, is associated with a depletion of intracellular ATP stores. In tumor models, deformities in sarcoplasmic reticulum and mitochondria alter ATPs' metabolic pathways in skeletal muscles, contributing to the energy deficit in cancer patients [73]. Asthenia is inextricably linked to cancer cachexia and its features. Thus, activation of non-profitable biochemical circles (e.g. Cori circle) and increased resting energy expenditure may multiply energy insufficiency in cancer patients. Fatigue mediated through ATP hypothesis is categorized as “physical” or “peripheral” fatigue [74].

## 47.4 Contributing Factors

Asthenia is frequently accompanied by several symptoms and conditions that contribute to its ontogenesis.

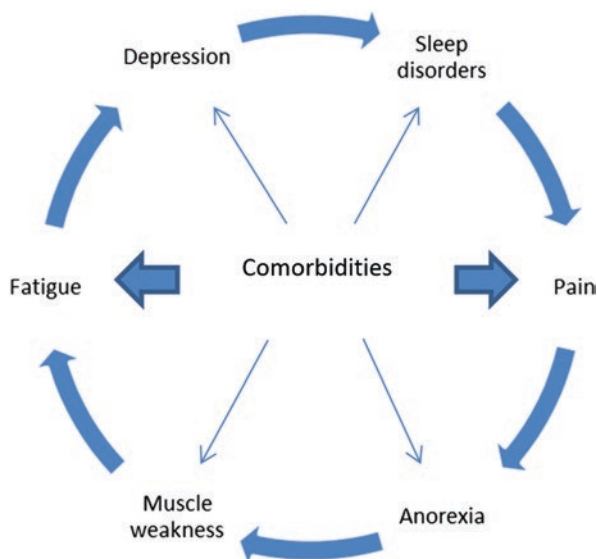
Anemia, a common consequence of cancer itself and its treatment, is recognized as a major contributor to fatigue [75] and its correction is associated with improvements in both fatigue and QOL [76]. However, in terminally-ill and bedridden patients, hemoglobin levels are not correlated with fatigue [77] and anemia is not considered a causative factor.

Cachexia and muscle wasting share common pathogenetic mechanisms with asthenia [78]. Cancer-cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass resulting in strength deterioration and exercise intolerance [79], contributing to the “asthenic” phenotype of cancer patients [80].

Other, often treatable factors include hypothyroidism, sleep disorders, pain, depression and other comorbidities. When present, all these factors form a vicious circle that enhances the debilitating character of asthenia (Fig. 47.1). According to the NCCN practice guidelines, all cancer patients reporting fatigue should be assessed as per the presence of all the above [81].

Treatment related factors are also associated with asthenia. Radiotherapy can lead to decreased blood counts, diminished food intake, nausea and vomiting, diarrhea and impaired absorption of food nutrients as well as increased levels of plasma pro-inflammatory cytokines, contributing to the emergence or increasing the severity of already established fatigue [82, 83]. Chemotherapy has been, also, linked with fatigue via various pathways. Besides myelotoxicity, neurotoxicity, cardiotoxicity,

**Fig. 47.1** Vicious circle of fatigue



gastrointestinal and direct CNS toxicity (intrathecal administration) [84, 85], chemotherapy can augment the development of cytokine-driven cognitive impairment [86]. Notably, different chemotherapy regimens induce different inflammatory responses [87]. Furthermore, hormonal changes related to certain treatment modalities in prostate [88] and breast cancer patients [89] are associated with fatigue. Moreover, interferon- $\alpha$ , a biologic response modifier, is known to cause fatigue and hypothyroidism in a substantial proportion of patients [90], while TKIs targeting the VEGF-receptor (sunitinib, sorafenib, pazopanib) are commonly related to fatigue development mostly via metabolic and gonadal, thyroid or adrenal function alterations [91].

Finally, medications used to alleviate symptoms in cancer patients such as opioids, antidepressants and certain anti-emetics (5-HT<sub>3</sub> antagonists, NK 1-receptor antagonists) are commonly associated with fatigue [92]. Drug intake on an as-needed basis or switch to other drug categories with less sedative action are useful strategies towards minimalizing asthenia's disabling impact on cancer patients.

## 47.5 Diagnosis and Evaluation

Albeit asthenia is an incapacitating symptom with severe effect on the patients' QOL, it is often undiagnosed or underdiagnosed and sorely undertreated. Often patients do not report it, believing that it is an inevitable or incurable consequence of cancer, while others underrate this symptom due to fear that their treatment would change or even stop. Another major issue is the defective doctor-patient communication. Patients often complain for the shortage of time available with their

physicians, while others don't want to be criticized as a "moaner". On the other hand, doctors underestimate the impact of asthenia on their patients' daily life and don't search for its presence. Even when patients report it, they decline fatigue as being an issue or encourage them to stoically accept it as an unavoidable and irremediable symptom of their illness [93, 94].

Hence, the first step in asthenias' management should be the identification of patients suffering from it. In an effort to optimally define and distinguish CRF from other overlapping symptoms, a multidisciplinary group of cancer treatment and supportive care experts together with patient advocates developed certain diagnostic criteria (Table 47.2). These proposed criteria from the Fatigue Coalition [95] have been evaluated in various patient groups and proven to be a useful diagnostic tool with strong validity and reliability [11, 96, 97]. Indisputably, these criteria represent a solid cornerstone that is safe to build on towards development of a common, universal scientific language.

It should be emphasized that there is no general consensus on the target population, the optimal method or the frequency to screen for CRF. According to the NCCN guidelines, which in their majority were subsequently adapted by ASCO as well, all cancer patients should be screened, beginning at the time of diagnosis and then at regular intervals during antineoplastic treatment. Cancer survivors should also be screened for fatigue as clinically indicated, at least once yearly [98, 99]. Use of single-item tools has been proven brief and sensitive enough for identifying patients in need of a more focused evaluation [100]. Hence, patients are asked to rate their fatigue on a scale of 0–10 (Table 47.3). Patients reporting mild fatigue require counseling and re-evaluation at regular time intervals. General measures for fatigue management could be applied. Patients reporting moderate or severe fatigue should proceed to further assessment with a detailed history, a physical examination and possibly a targeted laboratory evaluation. The aim of this in-depth approach to the patient with asthenia is to recognize any treatable contributing factors and to delineate its impact on different aspects of the patients' life (Table 47.4).

However, in order to receive a more comprehensive description of fatigues' "burden" other tools can be applied. A systematic review of the published literature revealed 14 different scales broadly used in cancer patients that met their quality inclusion criteria. Among them, the EORTC QLQ C30 subscale, the FACT-F and the FQ were the best validated [64, 101–108] (Table 47.5).

## 47.6 Treatment Strategies

On the grounds that asthenia is a multifactorial and multifaceted syndrome, our treatment approach should be multidisciplinary and multidimensional.

A team of healthcare professionals – including a physician, a nurse, a dietitian, a physiotherapist, a mental health professional and a social worker- should collaborate with the patient and his caregivers in order to create a supporting network with alleviating effect on the patients' symptom burden. Following a general –common for

**Table 47.2** Cancer-related fatigue: proposed diagnostic criteria

Proposed (1998 draft) ICD-10 criteria for cancer-related fatigue
<b>Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is (A1) significant fatigue.</b>
A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
A2. Complaints of generalized weakness or limb heaviness
A3. Diminished concentration or attention
A4. Decreased motivation or interest to engage in usual activities
A5. Insomnia or hypersomnia
A6. Experience of sleep as unrefreshing or nonrestorative
A7. Perceived need to struggle to overcome inactivity
A8. Marked emotional reactivity (eg, sadness, frustration, or irritability) to feeling fatigued
A9. Difficulty completing daily tasks attributed to feeling fatigued
A10. Perceived problems with short-term memory
A11. Postexertional malaise lasting several hours
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

Reproduced from *BMC Cancer*. 2011 Sep 6;11:387. doi: 10.1186/1471-2407-11-387. An examination of cancer-related fatigue through proposed diagnostic criteria in a sample of cancer patients in Taiwan. Yeh ET1, Lau SC, Su WJ, Tsai DJ, Tu YY, Lai YL

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all patients- approach, interventions for CRF could incorporate pharmacological or non-pharmacological measures as well as individualized treatment of an identified contributory factor.

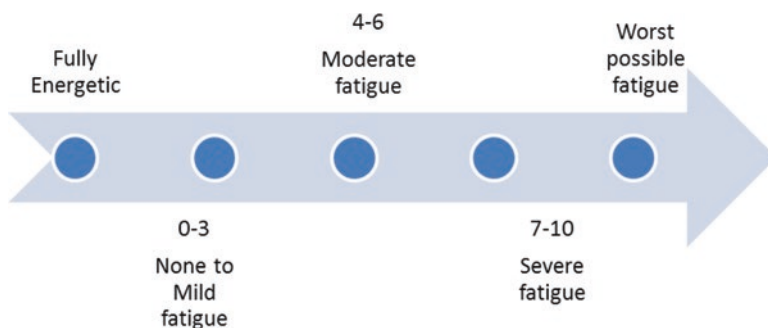
### 47.6.1 General Measures

Educating patients and their families about CRF could be beneficial [109, 110]. Even before the occurrence of asthenia, they should be informed about the incidence, the potential causes, the hazardous impact in various aspects of their daily



**Table 47.3** Fatigue quantification, self-reported severity scale

Fatigue	
Score	Severity
0–3	None to mild
4–6	Moderate
7–10	Severe



Numerical fatigue rating scale as the one used from Butt Z, et al

living and finally, the available general treatment strategies. The latter encompass various, chiefly shelf-applied modalities that could enhance one’s “defence” against fatigue development. Thus, energy conservation and activity management (ECAM), by giving priority to vital activities (e.g. hygiene) and postponing other less essential, can help patients regulate the usage of available energy resources [111]. Keeping diaries of the daily activities and of fatigue levels in certain time points can assist patients in scheduling their daily routine more efficiently. Additionally, a well-balanced diet ensuring a sufficient fluid, caloric, mineral and protein intake could also be beneficial.

Setting reasonable expectations, when confronting asthenia, is of paramount importance.

### 47.6.2 Treatment of Contributory Factors

All patients should be assessed for the presence of any treatable contributing factor (e.g., anemia, unrelieved pain, sleep disruption, or metabolic disorder). Upon identification, individualized therapeutic interventions should be applied as an initial approach to asthenia. Hence, anemia correction is associated with improvement in fatigue levels [76]. After declining other causes (e.g. blood loss, hemolysis), there are two options for anemia management: (i) red blood cell transfusions and (ii) use of erythropoiesis-stimulating agents in patients receiving chemotherapy [74] (Table 47.6). Furthermore, effective pain-control [112] and optimization of sleep disorders management [113] result in significant improvements in patient-reported fatigue.

**Table 47.4** Focused evaluation of patients reporting moderate or severe fatigue

Component	Description
History	Fatigue history: onset, time course, character, associations, relieving or exacerbating factors, impact on physical and cognitive capability, interference with ADL's, social life and emotional status.
	Review of systems: Identify conditions and symptoms that can guide physical examination and subsequent laboratory testing.
	Personal history: smoking, alcohol abuse, activity level, employment history.
	Medication history: Reveal contributing adverse effects or drug to drug interactions.
	Past medical history: Already diagnosed conditions that may act as contributing factors.
	Social history: Availability of caregiver support services.
Evaluation of disease status	Determine disease burden, treatment type and response to therapy. Consider disease progression.
Address all potentially treatable contributing factors	All patients should be assessed for the presence of anemia, depression or anxiety, unrelieved pain, sleep disorders and other comorbidities such as hypothyroidism, adrenal insufficiency, active infection or cardiac, renal, hepatic, pulmonary, gastrointestinal and neurological dysfunction.
	An initial laboratory work up should include complete blood count, a chemistry and electrolyte panel and TSH.
	Certain instruments could be used for pain or emotional distress assessment.
	If needed, consider referral to a relevant health care specialist.
Nutritional assessment	Check for alterations in body weight and composition.
	Evaluate the sufficiency of caloric intake.
	Check for fluid and electrolyte imbalances

NOTE: This list is not meant to be exhaustive

### 47.6.3 *Non-pharmacologic Interventions*

Non-pharmacologic interventions may include exercise, cognitive-behavioral and psychosocial interventions, nutritional consultation and mind-body interventions [98, 99].

The role of physical exercise in alleviating fatigue both, in patients undergoing treatment and post-treatment survivors, is well established [114]. Although susceptible to various bias (lack of randomization, selection bias, heterogeneity in exercise delivery and tools used to measure outcomes), a growing body of evidence supports the use of exercise in reducing CRF [115]. Various exercise programs have been studied, including aerobic, resistance training or a combination, with duration ranging from 1,5 to 6 months and frequency ranging from 2 times/weekly to 2 times/daily. While resistance exercise improves physical strength, a Cochrane review reported that only aerobic training significantly reduces fatigue levels [116]. Efforts are mounted towards determination of the optimal intervention, as an ongoing trial is evaluating the relative benefit of low versus high intensity exercise [117]. ASCO

**Table 47.5** Most important scales used for the measurement of cancer related fatigue

Instrument	Brief description
Brief Fatigue Inventory (BFI) ( <i>Mendoza TR, 1999</i> )	A 9 item visual analog scale validated in various tumor types and in different languages. Used primarily for the identification of patients suffering from severe fatigue. Unidimensional assessment tool.
Functional assessment of cancer therapy-fatigue (FACT-F) subscale ( <i>Yellen SB, 1997</i> )	Part of FACT-G used to measure health-related quality of life (QOL). A 13 item scale validated in various settings. Useful for detecting minimal but clinical significant alterations over the course of time.
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30) fatigue subscale ( <i>Aaronson NK, 1993</i> )	Part of a 30 item QOL questionnaire. A 3 item scale validated in various tumor types and multicultural settings. Easy to conduct. Useful mainly for the measurement of the physical dimension of fatigue. Inappropriate as the only measurement tool in terminally ill cancer patients.
Fatigue questionnaire (FQ) ( <i>Chalder T, 1993</i> )	An 11 item scale. Validated in various cancer types. Available comparative data between cancer patients and healthy controls. Easy to use. Evaluates physical and mental fatigues' dimension. Can be used on a daily basis.
Piper Fatigue Score-12 ( <i>Berger AM, 1998</i> ) ( <i>Piper BF, 1998</i> )	A 12 item scale. Shorter than the 22 item revised Piper fatigue score, which is validated in breast cancer patients. A multidimensional tool, with limited supporting data.
Cancer Fatigue Scale ( <i>Okuyama T, 2000</i> )	A 15-item scale, capturing physical and psychological aspects of fatigue. Not validated in English language.
Multidimensional Fatigue Inventory (MFI-20) ( <i>Smets EM, 1995</i> )	A 20 item scale. Validated in various tumor types but on small study populations. Multidimensional tool. Can be time-consuming.
Multidimensional Fatigue Symptom Inventory-short form (MFSI-30) ( <i>Stein KD, 1998</i> )	Part of a more comprehensive 83 item screening tool. A 30 item scale. Validated in various tumor types, mainly in breast cancer patients. Multidimensional tool. Can be time consuming. Limited data compared to other tools.

**Table 47.6** Risk and benefits of red blood cell transfusions and erythropoiesis-stimulating agent (ESA) use for the treatment of asthenia

	RBC	ESA
<b>RISKS</b>	Hypervolemia	Thromboembolic episodes (mainly when Hgb>12mg/dl).
	Acute transfusion reactions	Potentially adverse effect on patient clinical outcome. Not recommended for patients treated with curative intent.
	Viral infections	
	Iron overload	
<b>BENEFITS</b>	Rapid increase in hemoglobin levels	Reduced need for transfusion
	Rapid clinical improvement	Gradual increase in hemoglobin levels

endorses a weekly program of 150 min of moderate aerobic exercise (e.g. fast walking, cycling, or swimming) combined with 2–3 sessions of resistance training (e.g. weight lifting) for cancer survivors. However it should be noted that exercise programs should be tailored to the patients' functional capacity and comorbidities. While walking programs are thought to be safe for most cancer survivors, those with severe fatigue, cardiomyopathy, neuropathy or other conditions interfering with exercise tolerance should be referred to the appropriate specialist [99]. Exercise interventions have also been proved beneficial in patients undergoing chemotherapy as well as hospitalized patients with advanced cancer [118]. Nevertheless, it is obvious that such individuals cannot follow the recommended exercise program. Advanced cancer patients exhibit a wide variety of barriers that interfere with their capacity to exercise. These include disease related (lytic bone metastases, respiratory insufficiency due to extensive lung disease) treatment related (anemia, neutropenia and avoidance of crowded places, severe thrombocytopenia and risk of hemorrhage) and patient related factors (shortage of time, reluctance, discouraging caregivers). These patients should be encouraged to participate in individualized, less intense training programs with a propitious effect on QOL [119, 120].

Psychological interventions are also effective management techniques. These include various modalities such as psychotherapy, psychosocial counseling, stress reduction and relaxation techniques, energy conservation and cognitive-behavioral interventions. Their aim, through group therapy or individual counselling, is to infuse cancer patients with self-monitoring and self-care strategies to better cope with fatigue [121]. Behavioral therapies assist patients to realize the effect of negative thoughts on their perceptions and daily routine [122]. Their goal is to improve patients' functionality and self-dignity by manipulating the content of these thoughts. A review from the Cochrane database characterized these interventions as

promising in CRF management, concluding that actions focused specifically on fatigue are more effective than nonspecific [123]. Although several randomized trials have proven psychological interventions efficacy in patients during treatment [124] and in cancer survivors [125], some patients seem not to benefit [126]. Further research is needed to better define the optimal intervention on a specific target population, in the context of asthenia management.

Mind-body interventions principally include mindfulness-based stress reduction (MBSR), hypnosis, music approaches and yoga. There are limited data from randomized trials that these approaches, alone or in combination with other, may reduce fatigue in cancer survivors [122, 127, 128] and this benefit seem to be long-lasting (~6 months). Nevertheless, the role of other modalities such as acupuncture and moxibustion is equivocal. Although a handful of clinical trials report a positive effect [129, 130] the authors of a recent systematic review [131] concluded that the available data are not sufficient enough to draw a definite conclusion. Pilot studies have also suggested that Reiki [132] or even medical Qigong [133] may be beneficial. More high-quality randomized trials are needed to elucidate their role in asthenia management.

Finally, nutritional support by encouraging a balanced-diet with weight and body composition monitoring may be considered as an integral part of fatigue management [134]. Increased intake of green-leafy vegetables and tomatoes as well as a diet rich in whole grain and antioxidant nutrients has been linked with lower fatigue levels [135]. Referral to a dietician may be appropriate.

#### **47.6.4 Pharmacological Interventions**

Conflicting to the respectable amount of data regarding non-pharmacological approaches for CRF management, pharmacological interventions have not been meticulously studied in controlled trials.

However, various agents have been tested with inconsistent results throughout the heterogeneous trials [136]. The most extensively evaluated drug-classes are psychostimulants and other wakefulness-promoting agents, antidepressants and steroids.

From all the above mentioned agents, the authors of a recent systematic review [136] concluded that, only methylphenidate – a CNS stimulant- is associated with a moderate but significant ( $p = 0.005$ ) beneficial effect. Patients with more advanced disease and/or experiencing severe fatigue derived the most benefit [137]. Prolonged-treatment seems to display superior results compared to shorter duration programs with minimal side-effects, mainly vertigo and nausea [138]. Dexmethylphenidate and modafinil have also been linked with fatigue improvement compared to placebo. However, dexmethylphenidate resulted in a relatively high rate of drug-related adverse events [139], while modafinil probably only benefits patients with increased fatigue levels at baseline [140]. A therapeutic trial of psychostimulants should be undertaken in all patients, upon exclusion of other fatigue causes [98, 99].

In CRF-mouse models selective serotonin reuptake inhibitors (SSRI's) have been shown to improve depressive-like behaviors but not fatigue [141]. Correspondingly, a Cochrane review didn't document any benefit from these agents in 'fatigued' cancer patients [136]. Nevertheless, SSRI's have proven their efficacy in the management of depression and sleep disorders in patients receiving antineoplastic treatment [142, 143]. Contrarily, in small studies bupropion –an atypical antidepressant- has been linked with lower CRF levels [144, 145]. Larger, placebo-controlled studies are needed to clarify its role in fatigue management. Presently, antidepressants are not recommended in asthenia management [98].

Steroids have been used for alleviation of various symptoms in incurable cancer patients. Although their exact role in this setting is still controversial [146], low-dose steroids are widely accepted as valuable options in palliative care [147, 148]. Nonetheless, two recent studies reported that a short course of steroids (dexamethasone and methylprednisolone) was associated with significant improvement in fatigue scores compared to placebo [149, 150]. Unless contraindicated, a trial of steroids should be considered [98] in advanced cancer patients.

Moreover supplements such as American ginseng and guarana may reduce fatigue in patients undergoing chemotherapy without additional toxicity [151, 152]. However, ambiguous interactions between ginseng and other drugs interfering with CYP3A4 could be a serious hindrance to its use [153].

Finally, other agents such as donepezil [154], multivitamins [155], L-carnitine [156, 157], coenzyme Q10 [158], infliximab [159], etanercept [160] and thyrotropin-releasing hormone [161] have also been evaluated for their efficacy against CRF. However, results are subjected to various biases (small samples, non-randomized or open-label studies) and must be interpreted with caution. Randomized controlled trials are needed to bridge the specific gaps in the current knowledge.

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# Chapter 48

## Clinical Approaches to Adult Cancer Pain



Daniel Humberto Pozza, Sara Gil-Mata, Andreia Fontoura Oliveira, Alice Turner, Ramon Andrade De Mello, and Newton Barros

**Abstract** The disease course of cancer presents several physical manifestations, such as fatigue, nausea, vomiting or anorexia. However, the most feared symptom, with the greatest impact on quality of life is, undoubtedly, pain. Thus, pain relief is of paramount importance in any stage of the disease [van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. *Ann Oncol Off J Eur Soc Med Oncol/ESMO* 18:1437–1449, 2007].

**Keywords** Pain · Opioid · Palliative care

### 48.1 Introduction

The disease course of cancer presents several physical manifestations, such as fatigue, nausea, vomiting or anorexia. However, the most feared symptom, with the greatest impact on quality of life is, undoubtedly, pain. Thus, pain relief is of paramount importance in any stage of the disease [1].

Pain is a **multidimensional experience** that both is exacerbated and exacerbates depression and anxiety. Functioning impairment caused by pain leads to changes in subject's social role with serious consequences in quality of life. Cancer pain should

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be considered in the “**total pain**” concept in order to characterize the multidimensional nature of the palliative patient’s pain experience that includes physical, psychological, social, and spiritual domains [2]. Pain is related to a decreased ability to cope with the disease and there is increasing evidence that inadequate control may lead to poorer outcomes and increased mortality. The complexity of pain, especially in the context of an oncological disease with its strong emotional burden, imposes a **multidisciplinary and holistic approach** for optimal results.

Pain may be caused by the cancer itself or by its therapy, which includes not only chemotherapy and radiotherapy, common causes for chronic pain among this population, including cancer survivors, but also acute pain syndromes after surgery and/or other invasive procedures.

Despite the implementation of several guidelines for cancer pain management, including the well-known WHO recommendations, it is estimated that 5.5 million people suffering from cancer pain worldwide do not receive adequate treatment. This number may be an underestimation of the actual dimension of the problem due to a lack of statistical data, particularly in resource-limited countries, where cancer prevalence is increasing [3]. It is estimated that 43% of cancer patients have a negative Pain Management Index score, which means that nearly half patients are undertreated [4]. This is an extremely high percentage, with only a slight improvement tendency throughout the years [4]. Consequently, it is of paramount importance to analyse the barriers to a proper cancer pain control.

Women over 65 years of age without postsecondary education are at greater risk for pain under-treatment. Additionally, cultural minorities and patients on polymedication also tend to be undertreated. In the **disease factors**, adequacy of pain treatment usually varies according to tumour burden and functional status. There is a tendency to under-treat patients without metastatic disease or those who keep a good functional status. **Patients’ beliefs** also play an important role. They may believe that pain is inevitable, fear that it is a sign of disease progression or fear to be a burden to caregivers, thus under-reporting pain. On the other hand, non-adherence may be a result of poor treatment efficacy. Fear of side effects or of dependence may also be relevant and these may be an important concern for **healthcare providers** as well. Prescription errors due to lack of knowledge of equianalgesic doses, adjuvant analgesics and drugs’ mechanisms of action contribute to inadequate pain management. Education of patients, their family caregivers and healthcare professional is required to manage these barriers to provide optimal pain control [5]. In many countries there is also the need for a governmental commitment to overcome the over-rigid bureaucracy and lack of resources in order to allow pharmacologic prescription and education for physicians and opioid assessment for patients [6].

- Pain is a multidimensional experience that requires a **multidisciplinary and holistic approach** for optimal results.
- The **incidence** of pain among cancer patients is high, being many of them undertreated.
- Disease-related, patient-related and healthcare providers-related factors contribute for **pain undertreatment**.
- **Education** of patients, their family caregivers and healthcare professionals is required to manage these barriers to optimal pain control.

## 48.2 Pathogenesis of Cancer Pain

Cancer pain, despite being usually classified as inflammatory pain, is a distinct type of pain that induces a characteristic set of neurochemical changes in the spinal cord and sensory neurons. The specificity of these changes results of the complexity and dynamics of the cancer microenvironment. A tumour is made of different types of cells including not only malignant cells but also immune-system cells such as macrophages, neutrophils, T cells as well as endothelial cells and fibroblasts. These cells secrete several factors that sensitize primary afferent neurons, including nerve growth factor (NGF), proteases, prostaglandins, endothelin, bradykinin, protons, and tumour necrosis factor (TNF).

**Neurotrophic factors**, secreted by cancer cells themselves or by other cells of the cancer microenvironment, not only contribute to perineural invasion but also to pain. NGF, normally secreted to stimulate afferent sensory neurons growth and survival. However, NGF and its high affinity TrkA receptor are chronically increased in the tumour microenvironment [7]. Furthermore, tumour cells secrete **proteases** allowing its invasion, being protease activated receptor-2 associated with cancer pain [8].

**Prostaglandins** are pro-inflammatory lipids that result from cyclooxygenase (COX) action. Cancer cells and associated inflammatory cells express high levels of COX2 leading to increased prostaglandin production. Prostaglandins bind to prostanoïd receptors expressed by nociceptors causing their sensitization or directly exciting them [9, 10]. The same sensitization occurs as a result of the action of **endothelins**, vasoactive peptides expressed by several types of tumour, on endothelin receptor type A. These have been shown to be expressed on a subset of small unmyelinated primary afferent neurons [10]. **Bradykinin** is another vasoactive peptide implicated in cancer pain and its concentration is increased in some cancers that secrete kallikrein. Moreover, bradykinin directly induces increased secretion of endothelin-1 [7].

A **low pH** is a feature of the tumour microenvironment and results from increased metabolic rates and anaerobic conditions. An acidic pH sensitizes primary afferent nociceptors and activates several pH-sensitive channels, including the transient receptor potential vanilloïd-1 (TRPV1) channel. TRPV1 is a calcium permeable ionotropic receptor activated by stimuli such as heat, acid and protons. Antagonism of this channel has shown to reduce nociception [7]. In addition to the action of factors secreted by the tumour microenvironment on afferent nociceptors, tumour growth may directly entrap and damage nerves. **Mechanical injury**, compression, ischaemia and direct proteolysis of nerves, all contribute to cancer pain [9].

As chronic pain is established, **central sensitization**, affecting not only the spinal cord but also the forebrain, takes place. Astrocyte hypertrophy and up-regulation

of dynorphins are two mechanisms that have been associated with central sensitization. A decreased expression of glutamate re-uptake transporters is related to **astrocyte hypertrophy**, with a consequent excitotoxicity within the central nervous system. **Dynorphins**, on the other hand, seem to be abnormally expressed in the spinal cord leading to activation of neurons by non-noxious stimuli [9].

Lastly, it should be noted that the forebrain and amygdala, among others, can modulate the ascending conduction of nociceptive stimuli, explaining why patient attitude may influence the intensity of pain [9].

- **Neurochemical changes** sensitize primary afferent neurons, including **NGF, proteases, prostaglandins, endothelin, bradykinin, protons, and TNF**.
- Tumor growth can entrap and damage nerves contributing to cancer pain.
- **Central sensitization** contributes to pain development and maintenance.
- **Forebrain and amygdala** can modulate the ascending conduction of nociceptive stimuli, explaining why patient attitude may influence the intensity of pain.

### 48.3 Comprehensive Pain Assessment

Given the increasing importance and benefits attributed to pain relief in cancer patients, it is imperative that caregivers are up to date with the techniques of pain assessment, as well as, with best available therapies [11].

As previously discussed, oncologic pain may have different aetiologies. Thus, a comprehensive evaluation must be performed, not only to detect the presence, frequency, quality and intensity of pain, but also to discover its cause, which is essential to ensure the adoption of the most appropriate therapy [12]. In fact, failure to adequately assess pain and lack of documentation are often described as the greatest barriers to pain control, leading to a decrease in quality of life (QoL) [12, 13]. To minimize this situation, **screening of pain must be performed regularly**: all patients with cancer must be screened for pain during the initial evaluation, at regular follow-up intervals and whenever new therapy is initiated [12]. If pain is present, its intensity must be quantified whenever possible. However, assessing pain requires a more comprehensive approach, including patient's self-reporting of pain characteristics and its impact on daily life. It should be noted that given the inherently subjective nature of pain, reports by the patient should be the primary source when assessing pain [14]. Nevertheless, when communicative skills and cognitive function are severely compromised, external observation of pain-related behaviours and discomfort may be a preferable strategy [15].

There are several tools to assess pain severity. Regarding pain intensity, the most commonly used methods are numerical or categorical rating scales [12, 16]. However, given that some patients may experience difficulty using these scales

(especially children, the elderly or patients with different language or other communication barriers), other scales could also be used, such as the visual analogue scale or pictorial scale (The Faces Pain Rating Scale) [16–18]. Some practical strategies to achieve a more accurately cancer pain identification are asking about pain frequency and reconsidering threshold scores on pain intensity scales [19].

A method of particular interest when assessing pain severity is the Brief Pain Inventory (BPI), a formalized pain assessment tool which reflects the multidimensional nature of pain, assessing not only its intensity, but also the impact of pain on patient's life [11, 20, 21]. The BPI quantifies these measures through an 11 points numerical scale (from 0 to 10). Cut-points have been established to rate pain severity as mild, moderate or severe for the purpose of treatment planning [17, 21, 22]. It has been reported that pain interference with daily functions may be different in cancer patients compared with chronic non-cancer pain [20]. Indeed, the interference of pain in daily functions assumes an important role when assessing cancer-related pain and, in the same way as pain intensity, should be take into account when establishing therapeutic goals for comfort and function recovery [12].

If the Pain Rating Scale is above 0 and whenever important to the patient, a comprehensive approach is initiated, consisting of a thorough review of pain characteristics and clinical circumstances [12]. First of all, it is important to assess the complete history of pain, including features such as quality of pain, intensity and limitation on daily functions, onset and duration, location and radiation, temporal characteristics, course of pain, aggravating and relieving factors, instituted therapies, breakthrough or episodic pain uncontrolled by the current therapy, and associated features of the pain [12, 14]. Second, a psychosocial evaluation must be performed. Psychosocial state assessment is crucial for therapeutic success and should consider, among others, aspects such as the presence of psychological symptoms like depression or anxiety, indicators of psychiatric disorder, suicidal ideation, family function and patient's beliefs and preconceptions regarding pain management [14, 15]. However, psychosocial assessment is beyond the ambit of this review and should be thoughtfully studied. It is therefore essential to discuss patient expectations and concerns of pain management, in order to ensure an optimal therapeutic strategy [12].

Then, a complete physical examination and complementary analysis must be performed in order to exclude the presence of an underlying cause that requires specific therapy [12]. Those should include general medical and neurological examinations and a specific examination of the area of pain [14]. Without an appropriate treatment of the underlying cause, pain is unlikely to be well-controlled and in certain cases can get progressively worse reinforcing the importance of identifying the underlying cause of pain [12]. Thus, the ultimate aim of pain assessment is to identify the aetiology and pathophysiology of pain and proceed with the implementation of an individualized management plan that takes into account patient's clinical condition and expectations, optimizing QoL [12].

## 48.4 Management of Adult Cancer Pain

Comprehensive cancer pain treatment major goals are to decrease pain severity to acceptable levels, improve function and QoL and prevent the expected side effects of treatments [12, 23]. The most widely accepted algorithm for the treatment of oncologic pain continues to be based on the World Health Organization (WHO) guidelines for cancer pain control, proposed in 1986 [12, 15, 24]. The WHO approach states that cancer pain treatment should be based on a sequential three-step analgesic ladder: non-opioid analgesics should be used first, followed by weak opioids and then strong opioids, according to pain intensity [23, 25]. The goal was to provide a complete relief of pain, based on a simple public health tool that can be used all over the world [23, 24]. Despite having worked as an optimal teaching tool, the simplicity of this scheme is also its major drawback since the approach to oncologic pain is much more complex than this algorithm suggests [12, 23]. Thus, new courses of action have emerged to improve the effectiveness of pain control.

- Cancer pain treatment major goals are to optimize pain control, improve function and QoL and prevent the expected side effects of treatments.

## 48.5 Comprehensive Pharmacologic Management of Cancer Pain

### 48.5.1 General View

According to NCCN Guidelines for Adult Cancer Pain, the management of cancer-related pain is based on the distinction of three levels of pain intensity, using a 0–10 numerical or pictorial rating scale: mild (1–3), moderate (4–6) and severe (7–10) [12].

Pharmacologic analgesics, specially opioids, are the mainstay of cancer pain management [12, 23, 24]. When properly prescribed, opioids are very effective and well tolerated by most patients [23]. In addition to opioids, there are several drugs of interest for cancer pain treatment, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs, tricyclic antidepressants, NMDA antagonists, among others [24]. However, the goal of “freedom from cancer pain” [26] has not, and in some cases cannot, be achieved by the exclusive use of opioids and pharmacological adjuvants, being necessary to implement additional therapies [12, 23]. Non-pharmacologic integrative interventions (physical, cognitive behavioural and spiritual) are valuable options as most cancer patients experience a satisfactory relief from pain through an approach that includes primary antitumor treatments, systemic analgesic therapy and other non-invasive techniques such as psychological or rehabilitative interventions [12, 15]. Thus, all patients

experiencing pain should be provided with psychosocial support and begin educational activities [12].

- Pharmacologic analgesics, specially opioids, are the mainstay of cancer pain management.
- All patients experiencing pain should be provided with psychosocial support and begin educational activities.

The differences between pain related to an oncologic emergency and pain not related to an oncologic emergency as well as procedure-related pain and anxiety may be achieved.

**Pain related to an oncologic emergency** is defined as a life threatening event directly or indirectly related to a patient's cancer or its treatment. For example: pain due to bone fracture or impending fracture of weight-bearing bone, neuroaxial metastases with threatened neural injury, pain related to infection and acute abdomen due to obstructed or perforated viscous. The implementation of analgesic therapy for pain relief should be started simultaneously with the specific treatment for the oncologic emergency [12].

For the management of **pain not related to an oncologic emergency**, it is important to distinguish patients not chronically taking opioids on a daily basis (opioid-naïve) from patients who have previously or are chronically taking opioids for cancer pain relief (opioid-tolerant) [12].

### 1. Opioid-Naïve patients

#### (a) Management of mild pain [1–3]:

- begin treatment with nonopioid analgesics such as NSAIDs and/or acetaminophen, unless contraindicated [12, 15].
- consider treatment with slower titration of short-acting opioids if goals of function and comfort are not met with nonopioid analgesics [12].
- Note: it is imperative to proceed to a strict monitoring of NSAIDs side effects, as they can provoke severe toxicity such as gastrointestinal bleeding, platelet dysfunction and renal failure [15, 27].

#### (b) Management of moderate pain [4–6]:

- initiate short-acting opioids; compared with severe pain, the treatment of moderate pain should begin with slower titration of short-acting opioids [12].

#### (c) Management of severe pain [7–10]:

- initiate rapid titration of short-acting opioids [12].
- the route of administration must be selected according to the patient's analgesic needs [12].

- the management of the opioid common adverse effects should be started simultaneously with initiation of opioid therapy [12, 28].
- addition of adjuvant analgesic therapy for specific pain syndromes should be considered for all groups of patients to enhance the effects of opioids or NSAIDs [29].

## 2. Opioid-Tolerant patients

According to FDA, opioid-tolerant patients “are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.” [30, 31]

All patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long-acting formulation opioids with provision of a “rescue dose” to manage breakthrough or transient exacerbations of pain [12, 15].

## 48.6 Pharmacologic Interventions

When selecting the optimal analgesic strategy, physicians should take into account the patient’s pain intensity, any current analgesic therapy and concomitant medical illnesses. Therefore, an individual approach should be used to establish opioid starting dose, frequency and titration. Physicians should also be aware of potential drug-drug and drug-disease interactions while selecting the therapeutic plan [12].

## 48.7 Opioid Scheduling and Titration

Conventional practice is to provide an immediate opioid release formulation in order to relief pain as rapidly as possible [15, 28]. While starting opioid therapy, short half-life opioids are preferred as it is easier to speedily adjust the dose requirement and to manage possible side effects [12, 32]. After the titration period, all patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long-acting formulation opioids with prediction of a “rescue dose” to manage breakthrough or transient exacerbations of pain [12, 15].

In clinical practice, it is widely accepted that ongoing analgesic therapy should be administered in a regimen that includes the following methods: “around the clock”, “on demand” (in a dose escalation scheme), and “patient-controlled analgesia” [12, 23, 24]. For patients who have intermittent pain with pain-free intervals, immediate-release opioids can be administered on an “as needed” basis (except methadone due to its long duration of effect) [12].



With regard to breakthrough pain, short-acting opioids with a rapid onset and short duration are preferable [12, 15]. The rescue dose is usually equivalent to 10%–20% of the total daily dose given every hour as needed [12]. Several RCTs suggest that buccal, sublingual and oral/nasal transmucosal formulations are effective options to deliver rapid-acting opioids on demand for managing episodic breakthrough pain [24, 33, 34].

It should be emphasized that the repeated need for rescue doses per day may indicate the need to adapt the baseline treatment [12, 15]. If pain is inadequately controlled or persistent unmanageable adverse effects from current therapy occur opioid rotation should be considered [12].

- Short-acting opioids are the drugs of choice while initiating opioid therapy.
- All patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with long-acting formulation opioids with prediction of a “rescue dose” to manage breakthrough pain.
- Ongoing analgesic therapy is often based in the following methods: “around the clock”, “as needed” and “patient-controlled analgesia”.
- The repeated need for rescue doses per day may indicate the need to adapt the baseline treatment.

### **48.7.1 Route of Administration**

When prescribing the opioid therapy, it is important to select the least invasive and safest route of administration, which should be easy to be managed [12, 15]. The oral route should be the first choice in patients able to take oral medication, unless a rapid onset of analgesia is required or side effects arise due to oral administration [12, 28, 35, 36]. If the patient is unable to swallow or absorb drugs enterally, continuous parenteral infusion, either subcutaneous (SC) or intravenous (IV), is recommended [12, 14]. Compared with oral or transdermal, parenteral opioids provide faster and more effective plasma concentrations [12]. IV route is indicated for patients with severe pain when a rapid onset of analgesia is required because of the short lag-time between injection and effect [15, 37]. SC administration has a slower onset and lower peak effect comparing to IV but is considered equally effective, being a good alternative to oral delivery [12, 28]. Continuous SC infusion is also recommended for patients with dynamic pain states requiring frequent “rescue” doses for breakthrough pain [14].

Transdermal opioid patches may be considered as an useful alternative to continuous parenteral infusion when the oral administration is not feasible or tolerated or if the patient is noncompliant with oral opioids [14, 15, 28]. However, this route

is best reserved for patients whose pain requirements are stable due to the long duration of action of each patch [15, 28].

Note that when pain cannot be controlled by simpler means, epidural and intrathecal routes of administration of opioids should be considered as a way to improve effectiveness and minimize adverse effects, specially constipation and drowsiness [24].

- The oral route should be the first choice whenever possible.
- SC and IV infusions and transdermal patches are useful options.
- IV route is indicated when a rapid onset of analgesia is required.
- Epidural and intrathecal routes may be used when pain cannot be controlled by simpler means.

## 48.8 Selecting an Appropriate Opioid

Opioids differ in terms of their affinity to the receptors, pharmacokinetics and their physicochemical properties. Those properties give certain advantages to some over others due to differing side effect profile, routes of administration, development of tolerance and propensity for immunomodulation [38]. Indeed, the current trend of “opioid switching” is in part, driven by the need to interchange incompletely cross-tolerant opioids to minimize their inherent toxicities [39].

Pure agonists (such as morphine, oxycodone, oxymorphone and fentanyl) are the most commonly used medications in the management of cancer pain [12].

### 48.8.1 Morphine

- Morphine is considered the opioid of first choice for starting therapy and only a small percentage of patients are unable to tolerate oral morphine [12, 15, 40].
- Morphine can be delivered in multiple formulations and routes, including oral (preferable), parenteral or rectal [12, 15].
- For opioid-naïve patients, the recommendation is to provide 5–15 mg of oral short-acting morphine sulphate or equivalent as an initial dose [12].
- When converting from oral to parenteral morphine, the equivalent dose is one-third of that of the oral medication; upward or downward adjustment of the dose may be required to get an equianalgesic effect because of individual characteristics [41].
- **Beware:** morphine should be used with caution in patients with renal impairment as the accumulation of morphine-6-glucuronide (one of its active metabolites) may worsen morphine’s adverse effects, such as neurotoxicity [42, 43].

### **48.8.2 Fentanyl**

- Fentanyl can be delivery by the parenteral, spinal, transdermal, transmucosal, buccal and intranasal routes [44].
- Transdermal fentanyl is usually the treatment of choice in patients with stable pain who are unable to swallow, have reach unacceptable morphine toxicity, have gastrointestinal obstruction, or show poor compliance to oral therapy [12, 28]. Transdermal administration should only be used after pain is controlled by other opioids in opioid-tolerant patients [45].
- Transmucosal fentanyl is a good option for management of breakthrough pain in opioid-tolerant patients [12].

### **48.8.3 Hydromorphone**

- Hydromorphone is available in oral tablets, liquids, suppositories and parenteral formulations [44, 46].
- Hydromorphone has a consistent analgesic effect through the night. Thus it can be used in cancer pain patients with sleep disturbances [47].
- There is some evidence suggesting that the hydromorphone metabolite may lead to opioid neurotoxicity in a greater scale than the morphine metabolite. It is therefore important to use hydromorphone with caution in case of renal insufficiency [48, 49].

### **48.8.4 Oxycodone**

- Oxycodone is available in immediate- and extended-release formulations [50].
- Oxycodone is available in combination with acetaminophen. Regular monitoring should be carried out while using this formulation due to the risk of hepatic toxicity [12].
- Oxycodone is similar to morphine for adults' pain relief and can be used as first-line [51].

### **48.8.5 Oxymorphone**

- Oxymorphone is available in immediate- and extended-release formulations [50].

### **48.8.6 Methadone**

- Besides its agonist action on opioid receptors, methadone also acts as an antagonist at NMDA receptors [12].
- Methadone is commercially available in oral tablets or oral solution [52].
- Methadone's usage is difficult to manage in cancer patients due to inter-individual variation in pharmacokinetics, presenting a long half-life that ranges from 8 to more than 240 h [53].
- Methadone should be started at doses lower than those calculated and slowly titrated while monitoring for adverse effects and drug accumulation [12].
- There is evidence that methadone has similar analgesic efficacy and tolerability to morphine for treating cancer pain [54, 55].
- A retrospective observational study suggested that very-low-dose methadone associated with adjuvant haloperidol can provide proper pain control without opioid-induced hyperalgesia or required opioid dose escalation [56].
- High doses of methadone are thought to provoke QTc prolongation and torsades de pointes [57–59]. Indeed, the NCCN Panel recommends a baseline and follow-up echocardiogram for: (a) patients treated with methadone doses higher than 100 mg/day; (b) patients with cardiac disease; or (c) when methadone is used in patients receiving other medications also known to prolong QTc. If QTc is greater than or equal to 450, methadone dose may need to be reduced or discontinued [12].

### **48.8.7 Levorphanol**

- Levorphanol has a similar mechanism of action than methadone, but has a shorter half-life and a more predictable metabolism [60].
- For certain populations, like the elderly, levorphanol may be as beneficial as methadone but with diminished prescribing complexities and adverse effects [61]. One study also describes the potential efficacy of levorphanol in the treatment of neuropathic pain [62].

#### **48.8.7.1 Tramadol**

- Tramadol is indicated for treating mild to moderate pain [63].
- This drug is available in immediate- and extended-release formulations and is less potent than other opioids [12].
- It should be avoided in patients taking selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants, as tramadol inhibits the reuptake of norepinephrine and serotonin [12].

- The maximum daily dose is 400 mg for adult cancer patients and should be reduced in patients older than 75 years or in case of hepatic and/or renal dysfunction to reduce the risk of seizures [12].
- Despite there's one observational study stating that high-dose tramadol has an analgesic efficacy comparable to low-dose morphine but with lessened side effects [64], in a double blind study of cancer patients tramadol produced more adverse effects than hydrocodone and codeine [65].

### 48.8.8 Tapentadol

- Tapentadol is indicated for treating moderate to severe pain [12].
- Tapentadol also inhibits the reuptake of serotonin, which should be taken into account in patients taking SSRIs.
- The recommendation for maximum daily dose is 500 or 600 mg for the extended and the immediate release formulations, respectively, due to lack of published data regarding higher doses [12].
- Although no randomized trial evaluating the efficacy of tapentadol in cancer patients is available to date, a small prospective study in cancer patients showed that 100 mg of daily tapentadol was well tolerated and effective in decreasing pain intensity and improving QoL comparing with the placebo [66].

### 48.8.9 Buprenorphine

- Transdermal buprenorphine has been approved for chronic pain and there's increasing data supporting its use in cancer-related pain [67–69].
- If administered to patients currently taking a high-dose opioid, buprenorphine may precipitate a withdrawal crisis [12].
- Because buprenorphine may lead to QTc prolongation, FDA guidelines recommend a maximum dose of 20 µg per hour.

In the presence of renal impairment all opioids should be used with caution and at reduced doses and frequency. **Buprenorphine is the safest opioid in patients with chronic kidney disease** when the estimated glomerular filtration rate is <30 ml/min [15].

### 48.8.10 Equianalgesic Doses of Opioids

There are two situations in which equianalgesic doses of opioids must be calculated: (1) when patients step up from a weak opioid to morphine and (2) if there is need to switch between strong opioids [28]. Despite there is no high quality evidence to

support this practice, opioid switching should be considered in clinical practice as a mean to improve pain relief and/or drug tolerability [70]. It is recommended to consider opioid switching if pain is inadequately controlled or persistent adverse effects from current therapy occur [12].

The following agents are not recommended for cancer patients:

1. Mixed agonist-antagonists: the association of mixed agonists-antagonists with opioid agonists is not indicated for cancer pain treatment; converting from a pure opioid agonist to an agonist-antagonist may precipitate a withdrawal crisis;
2. Meperidine: meperidine is contraindicated for chronic pain;
3. Placebos: use of placebo in cancer patients is considered unethical.

## 48.9 Recommendation for Initiating/Usage of Short-Acting Opioids According to the NCCN Panel

- For opioid-naïve patients experiencing pain intensity  $\geq 4$  (or a pain intensity less than 4 but whose goals are not met): provide an initial dose of 5–15 mg of oral morphine sulphate or 2–5 mg of IV morphine sulphate or equivalent.
- For opioid-tolerant patients experiencing breakthrough pain intensity  $\geq 4$  (or a pain intensity less than 4 but whose goals are not met): calculate the previous 24-hour total oral or IV opioid requirement and increase the new rescue dose to an opioid dose equivalent to 10% to 20% of total opioid taken in the previous 24 h.
- Assess the efficacy and adverse effects every 60 min for orally administered opioids and every 15 min for intravenous opioids to determine the subsequent dose:
  - (a) If the pain score remains unchanged or is increased, it is recommended to increase the dose by 50%–100% of the previous opioid dose.
  - (b) If the pain score decreases to 4–6 (moderate pain), the same opioid dose is repeated and reassessment is performed at 60 min for oral opioids and every 15 min for IV opioids.
  - (c) If inadequate response is seen in patients with moderate to severe pain, upon reassessment after 2–3 cycles of the opioid, changing the route of administration from oral to IV or subsequent management strategies can be considered.
  - (d) If the pain score decreases to 0–3, the current effective dose of opioid should be administered “as needed” over an initial 24 h period before proceeding to subsequent management strategies.

## 48.10 Subsequent Management of Cancer Pain

Subsequent treatment continues to be based on pain intensity levels and consists in regular doses of opioids administration with rescue doses prediction, side effects management, and psychological and educational support [12]. According to the NCCN guidelines for adult cancer pain:

- If the pain is Severe, unchanged or increased
  - Comprehensive reassessment of pain must be performed with diagnosis re-evaluation and adjustment of the therapeutic plan.
  - Dose escalation of the current opioid is a common option.
  - If dose escalation is intolerable due to side effects, an alternative opioid can be selected
  - Addition of adjuvant analgesics should be considered to improve the opioids' analgesic effect or, when possible, to minimize the associated adverse effects [71].
  - Nonpharmacologic integrative interventions such as physical, cognitive and spiritual are useful tools and should be considered.
  - Additional interventions for specific cancer pain syndromes and specialty consultation must be considered.
- If the pain is Moderate and there is adequate pain relief
  - The current titration of the opioid may be continued or increased.
  - Addition of adjuvant analgesics, additional interventions for cancer pain syndromes and specialty consultation should also be considered.
- If the pain is Mild
  - Maintain the current titration of the opioid.
  - If there is adequate analgesia but intolerable side effects, the analgesic dose may be reduced by 10–25% of the current opioid dose.
  - Addition of adjuvant analgesics is also an option.
- If goals for comfort and function have been accomplished and 24-hour opioid requirement is stable
  - The conversion to an extended-release formulation is recommended, preferably with oral delivery whenever feasible.

Although most patients with cancer pain are well managed with traditional and adjuvant analgesics, there are a significant minority in whom this is inadequate or limited by adverse effects. For these patients the usage of interventional techniques plays a critical role in a multimodal symptom control approach [72].

## 48.11 Management of Procedure-Related Pain and Anxiety

Procedure-related pain represents an acute short-lived experience that may be accompanied by a significant degree of anxiety [12]. Fear, anxiety, depression and lack of sleep have been reported to increase pain and suffering in people with cancer [73, 74]. Thus, a proper control of anxiety may lead to a better pain control.

When selecting a strategy to manage procedure-related pain, one should consider the type of procedure, the anticipated level of pain and other individual characteris-

tics of the patient, such as age and physical condition, with these interventions including pharmacologic and/or nonpharmacologic approaches [12]. Nonpharmacologic interventions, including physical and cognitive modalities, are being implemented as a means to increase hope and reduce helplessness that many patients experience [12].

### ***48.11.1 Management of Anxiety***

Pre-procedure patient education is the key to minimize anxiety, as patients usually tolerate procedures better when they know what to expect. It should include procedure details and pain management strategies, allowing the patient to express his/her preferences in the selection of the analgesic approach. When feasible, anxiolytics should be given preemptively for control of procedure-related anxiety, preferably those with short time of action [12, 75].

### ***48.11.2 Management of Pain***

Supplemental doses of analgesics should be given in anticipation of procedure-related pain. Local anaesthetics can also be used to manage procedure related pain: physical approaches that may accelerate the onset of cutaneous anaesthesia include cutaneous warming, laser or jet injection and ultrasound. Sedatives may also be used [12].

### ***48.11.3 Reassessment of Cancer Pain***

Reassessment of pain must be obtained at specified intervals. Routine follow-up should be performed at least daily for inpatients and at each outpatient subsequent contact [12]. Still, the frequency will depend on patients' individual circumstances and institutional standards and may be increased in certain situations such as: at the onset of new pain (and according to its severity and level of distress), if there are changes in pattern or intensity of established pain and when a major therapeutic intervention is performed [14, 76]. The educational support is critical in this process, and, whenever possible, patients and caregivers should be taught and encouraged to use a pain diary to monitor pain levels and medication requirements, effectiveness and side effects [77]. Reevaluation is therefore essential to ensure that the analgesic therapy is having the maximum benefit with as few adverse effects as possible [12].

It must be emphasize that any change in the pattern of pain or any new report may be a sign of modification in the underlying pathological process [24]. For that



reason, a comprehensive assessment of pain and diagnostic evaluation must be performed following any new complaint and may require a review of the pain management plan [12, 24].

- Avoid Mixed agonist-antagonists, meperidine and placebos.
- Control of anxiety may lead to a better pain control.
- Reassessment of pain must be obtained at specified intervals.
- Encouraged to use a pain diary.

## 48.12 Opioid Adverse Effects

Opioids are associated with several adverse effects, including constipation, nausea, vomiting, pruritus, respiratory depression, motor and cognitive impairment, delirium and sedation. 10–20% of patients treated with opioids will find these adverse events intolerable. These may be severe enough to impose opioid switching, a certain route of administration or the use of adjuvant therapies [78, 79].

The prevalence of **constipation** among patients treated with opioids is high enough to justify a prophylactic approach. The NCCN guidelines recommend, therefore, the administration of a stimulant laxative with or without a stool softener with an escalating dose until one bowel movement per day or every 2 days is achieved [80]. The importance of an adequate fluid and dietary intake should also be stressed.

If the previous measures fail, bowel obstruction should be ruled out. Then, adding osmotic laxatives, bisacodyl or magnesium-based products should be considered. Prokinetic agents, although their prolonged use is not recommended due to an increased risk of neurologic complications, can be helpful, as well as enema with fleet, saline or tap water [80]. There is no evidence that one laxative should be preferred over the others and a combination of drugs with complementary mechanisms of action is likely to be more effective than a single agent [81].

When none of the above is sufficient, an opioid antagonist should be considered. Methylnaltrexone, which acts on gastrointestinal receptors, is administered by a subcutaneous injection. Opioid switching to fentanyl or methadone and performing other interventions in order to reduce opioid dosage can help to reduce this adverse effect [12].

**Nausea and vomiting** are present in up to 40% of patients receiving opioids [81]. When nausea is present, causes other than opioid therapy should be first assessed. Benzodiazepines or dopamine receptor antagonists, prescribed as needed, are effective options. If nausea persists, an around the clock regimen is the preferred approach and combining therapies with different mechanisms of action can provide an appropriate relief. Opioid rotation is to be considered when nausea persists for more than a week. Changing the route of administration from oral to transdermal or parenteral or reducing opioid dosage may also be useful [82].

**Pruritus** affects 10% to 50% of patients receiving opioids, especially early in the course of treatment [12]. Antihistamines, such as diphenhydramine or promethazine, may provide a considerable relief and, when not effective, opioid antagonists can be administered. These are the most effective treatment option but they decrease analgesia, which limits their prescription. Careful dose titration is required in order to maintain analgesic efficacy. Efficacy of other drugs has not yet been established [83].

Opioid-induced **sedation**, a well-known adverse effect, is thought to be caused by the anticholinergic action of these drugs. It can be a cause of inadequate dose escalation to achieve proper pain control, although tolerance to this effect often develops. If sedation persists for more than a week, it should be managed by opioid dose reduction, opioid rotation or psychostimulants. Although dextroamphetamine, donepezil, modafinil and caffeine are valid options, methylphenidate is the therapy of choice, since it is the most studied psychostimulant [84]. These drugs should be taken in the morning or early afternoon only to avoid insomnia.

**Sleep disturbances** although its clinical relevance is not well established, since other conditions related to the base disease could be the main cause. Nevertheless, opioids interfere in neurotransmitters balance – including GABA, serotonin, nor-adrenalin or dopamine –, all related to sleep regulation. Morphine is thought to reduce REM sleep through GABAergic signalling modulation by inhibiting acetylcholine release in the medial pontine reticular formation, which may affect wakefulness [84].

A syndrome of sleep-disordered breathing, with features of central sleep apnoea, can develop in long-term opioid therapy and should be addressed whenever the risk of this disturbance is relevant. The optimal treatment approach remains unclear but reducing opioids dosage may be helpful, as well as non-invasive positive airway pressure ventilation [85].

**Urinary retention** is particularly associated with epidural opioid analgesia, although it may develop even when oral or sublingual opioids are prescribed [84]. Naloxone and its analogues, despite being very effective, are not indicated for the treatment of urinary retention, since they reverse the analgesic effects of opioids. Further investigation is required to assess the effects of other opioids antidotes in this context [86].

Opioid **endocrinopathy** refers to a cluster of hormonal effects related to opioid use. These have shown to influence the function of several hormones, including testosterone, oestrogen, luteinizing hormone and gonadotrophin releasing hormone. Sexual dysfunction, depression, fatigue and accelerated bone loss may be a consequence of opioid-induced hypogonadism. In selected cases, hormone replacement may be appropriate, although there is a lack of studies evaluating its benefits [84, 87].

Long-term use and high doses of opioids are associated with an increase in pain sensitivity or **hyperalgesia** [88]. Unfortunately, there is no effective treatment for opioid-related hyperalgesia. When hyperalgesia is suspected, opioid switching or

dose reduction seems to be the only adequate approach. In addition, no opioid has shown to be associated with a lower risk of hyperalgesia development [89].

**Delirium** is a condition characterized by a disturbance of consciousness, cognitive and perception dysfunction and altered psychomotor behaviour. It occurs in 26%–44% of cancer patients admitted to hospital and towards the end of life it is experienced by over 80% [90].

Opioids daily doses of <90 mg seldom cause delirium [91]. Nevertheless, during opioid titration, a neuroleptic drug, such as haloperidol or risperidone, may be useful. Whenever these prove not effective, opioid switching is recommended [12].

**Respiratory depression** can be a consequence of opioids administration, presenting with low respiratory rate and low oxygen saturation. Once it is established, oxygenation and decrease of opioid dose should be the first approach. If these measures fail to revert hypoxia, then naloxone, an opioid antagonist, should be administered. A careful titration is recommended, with an intravenous dose of 20–100 µg every 2 min. There is a risk of acute withdrawal syndrome onset, if opioid tolerance has already developed [92, 93].

Respiratory depression may be a major concern when patients have comorbidities which cause a decrease in cardiopulmonary reserve. It should be noted that, among these patients, hypercapnia occurs before hypoxia [12].

- Prophylactic approach of **constipation** may be used with stimulant laxative with or without a stool softener. If these fail, osmotic laxatives, bisacodyl, magnesium-based products, prokinetic agents and an opioid antagonist are other therapeutic options.
- Benzodiazepines or dopamine receptor antagonists are recommended for the control of **nausea** and for refractory cases opioid rotation or a different administration route may be considered.
- Antihistamines, such as diphenhydramine or promethazine, may provide a considerable relief for **pruritus** and, when not effective, opioid antagonists may be an option.
- If **sedation** persists for more than a week, it should be managed by opioid dose reduction, opioid rotation or psychostimulants.
- **Sleep-disordered breathing** can be managed by reducing opioids dosage or by using non-invasive positive airway pressure ventilation.
- The use of opioid antagonists is not recommended for **urinary retention** treatment.
- During opioid titration, a neuroleptic drug, such as haloperidol or risperidone, may be useful if **delirium** develops.
- If **respiratory depression** develops, oxygenation and decrease of opioid dose should be the first approach. If these measures fail to revert hypoxia, then naloxone should be administered.

## 48.13 Tolerance and Dependence

Tolerance to opioids is defined as the requirement of increased doses to maintain the same analgesic effect. Tolerance may also develop to side effects, with reduced nausea, vomiting, respiratory depression and sedation over the course of therapy. No tolerance to constipation, however, is observed [24].

Analgesic tolerance can be innate, that is, genetically determined and present on the onset of treatment, or acquired. Acquired tolerance may be explained by several factors. Pharmacokinetic changes may result from altered metabolism of the opioid by induction of related enzymes. On the other hand, desensitization and down-regulation of opioid receptors with continuous administration of the drug are believed to be the major mechanisms that induce pharmacodynamics-mediated tolerance [89, 94].

It should be noted that not only chronic, but also acute, opioid administration is related to tolerance development. This has led to reluctance to prescribe opioids, which would be preferably saved for cases of severe pain, based on the fear that they wouldn't be effective when they would be needed the most. Several studies, however, have shown that this fear is unjustified, contributing to pain under-treatment with its well-known consequences [84].

Furthermore, **cross tolerance**, that is, the development of tolerance on one specific opioid that results in tolerance to others, may be incomplete. The overall action of a particular opioid is the result of its action on different receptors, mainly mu receptors, which, in turn, have different subtypes. Those differences in action can be explained by different affinity degrees of each particular opioid for each receptor subtype. Thus, when a new opioid is introduced, a new selectivity pattern will be present, explaining incomplete cross-tolerance [89]. It is of the utmost importance that clinicians are well aware of that fact, in order to prevent overdosing when switching opioids. Safety of equianalgesic dose tables is not guaranteed, since it is unpredictable whether different receptor selectivity of a distinct opioid will lead to complete, partial or no cross-tolerance at all. In fact, pharmacogenetics determines relative potency, effectiveness and safety of each opioid for each patient and since genetic testing is not routinely available, clinicians must assume that every patient is potentially at risk for overdose when opioids are switched [95].

Another common concern among patients and physicians is the development of **dependence and addiction**. Dependence may occur in many patients and may be physical or psychological. If physical, it may result in withdrawal syndromes when dose is reduced. Psychological dependence, on the other hand, relates to the fear of pain worsening or recurrence upon opioid reduction or postponement. This can lead to increased requests for opioids, a behaviour which should not be mistaken for addiction. In fact, when addiction is present, a rare condition in a pain management context, there is a lack of compliance when opioids are switched or replaced by non-opioid analgesics, even if an optimal pain control is achieved. Although withdrawal syndromes are often present when dependence or addiction are established, they don't necessarily mean these have actually developed [24, 96]. While these concerns

should not be impeditive for an adequate pain management, opioids should be prescribed carefully. In order to reduce the risk of misuse, addiction and overdose, the FDA has established **Risk Evaluation and Mitigation Strategy (REMS) programs** for selected opioids [97].

- Analgesic **tolerance** can be innate or acquired. Acquired tolerance may be explained by pharmacokinetic changes and by desensitization and down-regulation of opioid receptors with continuous administration of the drug.
- **Cross tolerance** may be incomplete and, consequently, overdose may occur when opioids are switched.
- Opioid **addiction** is a rare condition in a pain management context.

### 48.13.1 Non-opioid Analgesics

The WHO ladder for the management of cancer pain recommends the use of a non-opioid analgesic for mild pain and continuing its administration with the onset of moderate pain as adjuvant analgesia. While drugs as paracetamol and NSAIDs have shown efficacy in treating cancer pain, it is questionable whether its combination to opioid analgesics is superior to opioids alone or not [98–100]. Consequently, clinical practice varies widely among different countries, being the maintenance of acetaminophen when opioid therapy is started the current practice in Europe [101].

**Acetaminophen** is effective for the treatment of mild cancer pain, has a good safety profile and is inexpensive. Hepatotoxicity is rare even in the presence of chronic liver disease, as long as a daily dose of 8 g is not exceeded. Concerns about hepatic and renal toxicity are mainly due to the inclusion of acetaminophen in several opioid preparations. Recommended daily dose by the FDA is 4 g with a limit of 325 mg per tablet in prescription products to reduce the risk of hepatic injury. Also, it should be kept in mind that chronic alcohol abuse predisposes patients to hepatic toxicity, as does prolonged fasting. Severe hypersensitivity reactions to acetaminophen are uncommon [101].

Most NSAIDs are non-selective COX inhibitors. While selective COX 2 inhibitors, such as celecoxib, have a better **gastrointestinal toxicity** profile, they increase the risk of **cardiovascular events**, including myocardial infarction and stroke, due to their prothrombotic action. According to the NCCN guidelines, naproxen and ibuprofen are the elected NSAIDs when increased risk of cardiotoxicity is present. The overall risk of NSAIDs – including hepatotoxicity, nephrotoxicity and gastrointestinal bleeding is increased in patients with comorbidities and in the elderly [12]. *Helicobacter pylori* infected patients may benefit from its prior eradication and proton pump inhibitors or misoprostol may be prescribed to those with peptic ulcer [101]. Caution should be taken in prescribing NSAIDs with anticoagulants since the **risk of haemorrhage** is significantly increased.

- **Acetaminophen** is effective for the treatment of mild cancer pain, has a good safety profile and is inexpensive. Hepatotoxicity, although rare, is the main safety concern.
- **NSAIDs** are associated with gastrointestinal toxicity, cardiovascular events and haemorrhage and should be prescribed with caution to patients at higher risk of developing such complications.

## 48.14 Management of Bone Pain

Several cancer types, including some of the commonest, such as breast, prostate or lung cancer, have a predisposition to metastasize to bone. Once metastases are present in bone, pain will be a symptom in up to 45% of patients [102]. The location and extent of metastases do not, however, correlate to pain severity and many patients with widespread bone involvement only report mild pain [102]. Bone pain initially presents as dull but gradually grows in intensity. As the cancer burden within bones extends, breakthrough pain may emerge, which can occur spontaneously or triggered by movement. Owing to its severity and unpredictable behaviour, the management of bone pain may be particularly challenging [103].

Specific therapeutic strategies have been developed as the mechanisms underlying cancer-induced bone pain became clearer and the available options are currently wide. Multiple fraction regimens of **radiotherapy** are the gold standard treatment of cancer-induced bone pain [104], although it is estimated that only about 25% of patients report a complete pain relief [105]. The remaining cases will require an alternative or complementary approach.

Clinical trials have demonstrated that **bisphosphonates**, such as zoledronic acid, and denosumab, a RANKL inhibitor, not only prevent skeletal related events (SRE), such as fractures and spinal cord compression, but also have a beneficial effect on metastatic bone pain [106–110].

**Neurochemicals** such as prostaglandins, nerve growth factors and endothelins are released by tumour cells, all contributing to initiate and maintain bone pain. Prostaglandin synthesis is blocked by **NSAIDs**, and selective COX 2 inhibitors, at least in laboratory models, have shown to reduce bone destruction and cancer-induced bone pain [111].

**Surgical treatment**, as well as **ablative interventions**, such as radiofrequency or ultrasound ablation may also be performed to reduce SRE and bone pain. Non-pharmacological interventions will be discussed later.

- Owing to its severity and unpredictable behaviour, the management of bone pain may be particularly challenging.
- Multiple fraction regimens of **radiotherapy** are the gold standard treatment of cancer-induced bone pain.
- **Bisphosphonates** and **denosumab** prevent SRE, such as fractures and spinal cord compression, and have a beneficial effect on metastatic bone pain.
- **NSAIDs** seem to reduce bone destruction and cancer-induced bone pain.
- **Surgical treatment**, as well as **ablative interventions**, such as radiofrequency or ultrasound ablation, may also be performed to reduce SRE and bone pain.

## 48.15 Neuropathic Pain

Cancer-related neuropathic pain results from damage to the somatosensory nervous system caused by the disease itself or from its treatment. It dramatically decreases quality of life, since it is usually severe and difficult to control and may impose treatment delays, switching or discontinuation [112].

The **prevalence** of neuropathic pain in the general population is well established, but not among cancer patients [113]. However, an early study reports that a neuropathic component is present in up to 39% of patients suffering from cancer pain, although a pure neuropathic pain is seldom present [114]. Its treatment is challenging requiring a longer time to be controlled and higher doses of opioids [113]. It usually presents as a background pain with triggered or spontaneous exacerbations. The affected areas may be afflicted by hyposensitivity, hypersensitivity or both. Paraesthesia, allodynia and dysesthesia may also be present. Painful peripheral polyneuropathy, with a typical glove and stocking distribution, may develop as a complication of some chemotherapeutic agents and, in most cases, is dose-dependent [115]. The pattern of sensory abnormalities can greatly vary between individuals, which has led to an attempt to identify subgroups of patients based on different phenotypic profiles, rather than on aetiology [116].

The multiplicity of sensory symptoms affecting individuals is likely to reflect the diversity of the underlying pain-generating mechanisms. In fact, several mechanisms, such as ectopic nerve activity and central sensitisation, can lead to neuropathic pain and many of these are found in different pathologies, which proves its complexity [117].

**Other intervening factors** in neuropathic pain onset and maintenance include inflammation, loss of inhibitory neurons and sympathetic fibres involvement [118–121].

Chemotherapy-induced neuropathy may be caused by several commonly used drugs (E.g.: Cisplatin, Oxaliplatin (chronic), Vincristine, vinblastine, vinorelbine, vindesine, Paclitaxel, Abraxane, Docetaxel) and its severity depends on dose, schedule and regimens. It can consist of axonopathy (when distal axons have been injured) or neuronopathy (when neurons of the dorsal root ganglia have been injured) the last being usually more severe and tending to be permanent. No therapy has been approved yet for its prevention or treatment [112].

Management of neuropathic cancer pain is mostly the same as that of non-malignant neuropathic pain. Its heterogeneity explains the poor response to conventional therapies. Adjuvant drugs are usually necessary and each drug should be introduced at a time and its dose should be progressively titrated in order to adequately adjust the dose according to patient's response and to monitor adverse effects [122].

**Anticonvulsants**, namely gabapentin and pregabalin, are widely used for the treatment of neuropathic pain. They act as antagonists of presynaptic voltage-dependent calcium channels, by binding at calcium channel alpha2-delta proteins, thus inhibiting neurotransmitters release at synapses [123, 124]. They are well-tolerated drugs with no known drug-drug interactions [115]. In addition, gabapentin has been reported to reduce radiation-related mucositis pain in cancer patients [125]. Carbamazepine and oxcarbazepine are earlier anticonvulsants that are still the first choice for trigeminal neuralgia but not for the treatment of cancer-related neuropathic pain, as they present an unfavourable adverse-effect profile and extensive drug-drug interactions [115].

Antidepressants, such as tricyclic antidepressants or selective serotonin norepinephrine reuptake inhibitors, have a beneficial effect in neuropathic pain.

**Tricyclic antidepressants** include secondary amines – such as desipramine and nortriptyline – and tertiary amines – such as amitriptyline and imipramine. These drugs have shown to be effective, leading to pain relief in a few days, with a number needed to treat of approximately 3 [126]. It must be noted, however, that the effect of this class of antidepressants has been established mainly for diabetic neuropathy and postherpetic neuralgia and only a limited number of studies are available for other neuropathic pain syndromes [126].

Sodium channels and voltage-dependent calcium channels are the main pharmacological targets of tricyclic antidepressants which explain their analgesic effect, along with serotonin and noradrenalin reuptake inhibition [127]. Presynaptic reuptake of these monoamines will increase their levels in the synaptic clefts, thus enhancing pain suppression by central nervous system pain modulation pathways [127].

The adverse effect profile of these drugs is highly variable due to genetic polymorphisms involving enzymes implicated in their metabolism and are mainly related to their anticholinergic effects. Doses should be initially low and careful



titration must be performed [117]. Contraindications to the use of tricyclic antidepressants include epilepsy, heart failure, and cardiac conduction blocks.

**Norepinephrine and serotonin reuptake inhibitors** (NSRI) venlafaxine and duloxetine are also effective in the treatment of neuropathic pain, in addition to their therapeutic role in depression, which often accompanies pain syndromes [122]. NSRIs are generally well tolerated and side effects tend to decrease during the treatment course. Blood pressure should be monitored when venlafaxine is prescribed, especially in patients with hypertension. Duloxetine, on the contrary, has no cardiovascular effects.

Clinicians must be aware that several antidepressants have an important inhibitory effect on cytochrome P450 enzymes, in particular CYP2D6. Active metabolites of tamoxifen, a commonly used drug in patients with hormone receptor-positive breast cancer, are a result from CYP2D6 action. Consequently, its inhibition may result in decreased tamoxifen efficacy and increased cancer recurrence [128]. Mild CYP2D6 inhibitors, such as venlafaxine, should be preferred over more potent ones, such as duloxetine or bupropion.

Although other drugs are usually preferred for the treatment of neuropathic pain, some studies suggest that **opioids** have a similar efficacy to antidepressants [129]. Since neuropathic pain may coexist with other types of pain and some patients may be intolerant to commonly prescribed adjuvant drugs, opioids can be a good option. Nevertheless, although they may be effective for neuropathic pain treatment, higher doses are usually required, possibly resulting in intolerable adverse effects for most patients [122].

**Lidocaine** blocks sodium channels on ectopic peripheral afferent fibres without causing numbness of the skin. Topical lidocaine is available as a 5% patch or gel. Although controlled clinical trials have been conducted mainly for postherpetic neuropathy and focal neuropathic pain, lidocaine patches have been used in clinical practice with good results [122]. It is particularly indicated for localised peripheral neuropathic pain. Systemic absorption is negligible and the only reported side effects are mild skin reactions.

The main adverse effects, mechanisms of action and dosage of non-opioid drugs used for the treatment of neuropathic pain are listed on Table 48.1.

Although the use of concomitant drugs is usually avoided due to the risk of additive side effects, drug-drug interactions and non-compliance, **combination therapy** may be useful for neuropathic pain control. Extended-release morphine combined with pregabalin or gabapentin have been successfully used. Nortriptyline with gabapentin or pregabalin with topical lidocaine are other combinations that have shown to provide a better pain relief than that achieved with each drug alone [117].

**Interventional therapies**, indicated for those patients who do not respond to pharmacological therapy, or only respond partially, are discussed later.

**Table 48.1** Common non-opioid agents for neuropathic pain treatment [108, 146]

Drug	Mechanism of action	Adverse effects	Precautions	Starting daily dose	Titration	Maximum daily dose
<b>Tricyclic antidepressants</b>						
Nortriptyline	Serotonin/norepinephrine reuptake inhibition;	Sedation;	Cardiovascular disease;	10–25 mg nightly	10–25 mg increase every 3–7 days	75–150 mg
Desipramine	Sodium channels block; Anticholinergic effect.	Dry mouth; Urinary retention; Weight gain	Glaucoma; Seizure disorder; Interaction with drugs metabolized by cytochrome P450 2D6			
<b>SSNRIs</b>						
Duloxetine	Serotonin and norepinephrine reuptake inhibition	Nausea; Xerostomia;	Hepatic and renal insufficiency; alcohol abuse, use of tramadol	20–30 mg	No evidence that higher dose is more effective	120 mg
<b>Calcium channel <math>\alpha_2</math>-<math>\delta</math> ligands</b>						
Gabapentin	Glutamate, norepinephrine, and substance P release inhibition	Sedation, dizziness, peripheral oedema, gastrointestinal symptoms.	Renal insufficiency	100–300 mg nightly or 3 times/day	100–300 mg every 1–7 days	3600 mg
Pregabalin	As gabapentin	As gabapentin	As gabapentin	25–50 mg 3 times/day	50 mg increase after 1 week	200 mg 3 times/day
<b>Topical lidocaine</b>						
5% lidocaine patch	Sodium channels block	Local erythema/rash	None	3 patches/day	Non-applicable	3 patches/day

- Ectopic nerve activity, central sensitisation, inflammation, loss of inhibitory neurons and sympathetic fibres involvement are the main mechanisms underlying neuropathic pain onset and maintenance.
- **Anticonvulsants** are widely used for the treatment of neuropathic pain with good results. They are well-tolerated drugs with no known drug-drug interactions.
- **Tricyclic antidepressants** have also shown to be effective, leading to pain relief in a few days. Doses should be initially low and careful titration must be performed since the adverse effect profile of these drugs is highly variable due to genetic polymorphisms.
- **NSRIs** are also effective in the treatment of neuropathic pain, in addition to their therapeutic role in depression, often associated with pain. Several antidepressants, though, have an important inhibitory effect on cytochrome P450 enzymes.
- Although **opioids** may be effective for neuropathic pain treatment, higher doses are usually required, possibly resulting in intolerable adverse effects for most patients.
- **Lidocaine** patches have negligible side effects and are a good option for localised peripheral neuropathic pain.
- **Interventional therapies** are indicated for those patients who do not respond to pharmacological therapy or who experience major drug adverse effects.

## 48.16 Pain Caused by Bowel Obstruction

Pharmacological treatment of bowel obstruction pain is indicated for inoperable patients and aims to relieve abdominal continuous pain as well as intestinal colic. The prescribed analgesics are mainly strong opioids, but for refractory colic hyoscine butylbromide or hyoscine hydrobromide, two anti-cholinergic drugs, may be used in association to opioids. The preferred routes of administration are subcutaneous, intravenous and transdermal [130].

## 48.17 Adjuvant Interventions

Interventional techniques consist of invasive approaches that provide temporary or permanent interruption of nerve transmission. Even when optimal pharmacological therapy is provided, it is estimated that 10% of patients suffer from refractory pain [131]. This corresponds, in most cases, to neuropathic and bone pain. For these patients, as well as for those who experience major adverse effects from analgesic therapy, those techniques may be useful, as part of a multimodal approach [132].

Many patients undergoing these procedures are being treated with high dose opioids. This implies the risk for respiratory depression and excessive sedation as a result of a successful intervention. Careful monitoring of respiratory function is therefore mandatory and an appropriate reduction of opioid doses must be performed. Often, half the usual dose is administered immediately after the procedure and a subsequent further reduction is performed in order to avoid a withdrawal syndrome [132]. Peripheral nerve blocks, neurolytic sympathetic blocks, neuraxial analgesia, vertebroplasty and kyphoplasty are the main interventional procedures for cancer pain relief.

## 48.18 Peripheral Nerve Blocks

**Peripheral nerve blocks with local anaesthetics** have a limited use in the management of cancer pain. However, they may be useful for acute pain control or to provide short-term analgesia while other therapeutic approaches are implemented. Acute pain control may be needed on the perioperative setting or for other acute events, such as pathological rib fractures, when an intercostal nerve blockade, by means of a bolus injection of local anaesthetics, may be beneficial. Alternatively, catheter infusions adjacent to nerve plexuses, such as the brachial plexus, or other peripheral nerves may provide pain relief for days or weeks. Implantation of catheters into the intrapleural space to anaesthetise the intercostal nerves, and, additionally, the thoracic sympathetic chain, is used, especially for post-thoracotomy pain control, although there are early reports of its use for pain control in the terminally ill patient, with good results in a selected population of patients [133, 134]. The onset of pneumothorax and the risk for local anaesthetic toxicity limits its use [135]. Furthermore, the presence of advanced malignant disease often distorts the normal neuroanatomy and, consequently, poses technical difficulties.

**Neurolytic blockade of peripheral nerves**, mainly intercostal nerves, although providing a prolonged pain relief, is associated with a high incidence of neuritis. This can trigger pain that is much more difficult to control than the original one and, thus, should be reserved for patients with a very short life expectancy when other strategies have failed [136].

Clinical reports on the use of peripheral nerve blocks are limited and the lack of comparative studies compromises the establishment of recommendations for clinical practice [136].

- **Single-shot peripheral nerve blocks** with local anaesthetics may be useful for acute pain control. Alternatively, catheter infusions adjacent to nerve plexuses or other peripheral nerves may provide pain relief for days or weeks.
- **Neurolytic blockade of peripheral nerves**, mainly intercostal nerves, although providing a prolonged pain relief, is associated with a high incidence of neuritis.

## 48.19 Autonomic Nerve Blocks

Autonomic nerve blocks consist of the blockade of sympathetic nervous system fibres, which carry pain afferents from the viscera. The most commonly performed procedures are celiac plexus ablation, superior hypogastric plexus block and ganglion impar block.

**Celiac plexus and splanchnic nerves block** is often used to control pancreatic cancer or other upper abdominal malignancies related pain. Although there is no robust statistical evidence of a better pain control than that offered by analgesic therapy only, the fact that this technique enables lower opioid doses and, consequently, fewer side effects justifies its importance [137].

The celiac plexus lies retroperitoneally at the level of the T12 and L1 vertebrae and anterior to the aorta and carries afferent fibres from several abdominal organs including the pancreas, liver, biliary tract and bowel up to the first part of the transverse colon. The most common access route is posterior with fluoroscopy guidance, although other approaches may be useful. The ultrasound-guided anterior approach is a minimally invasive technique with increasing popularity and is believed to be a safer procedure. Nonetheless, no randomized controlled trial has shown its superiority over other methods yet [137, 138].

Contra-indications to the use of this technique include severe refractory coagulopathy or thrombocytopenia, aortic aneurysm or mural thrombosis, local or intra-abdominal infection and bowel obstruction. Large masses making anatomical structures position difficult to visualize are a relative contraindication [139].

Possible complications of these methods include diarrhoea, temporary postural hypotension, back pain and dysaesthesia. More severe side effects, including permanent motor deficit, are rare [132]. Four cases of paraplegia were reported in a review of 2730 coeliac blocks, three of which with associated loss of anal and bladder sphincter function. These major complications were attributed to either direct spinal cord injury during the procedure or to spinal ischaemia secondary to anterior spinal artery spasm [140].

**Superior hypogastric plexus block** enables reduction of pain with lower abdominal or pelvic viscera origin. It carries afferents from the bladder, uterus, prostate, vagina, testes, urethra, descending colon and rectum. The hypogastric plexus lies retroperitoneally at the level of L5 and S1 vertebrae and its approach is most commonly posterior, with the patient in the prone position, under computed tomography and fluoroscopy guidance. However, an ultrasound-guided anterior approach may be useful since it can be performed with the patient lying supine and avoids radiation exposure [141]. A transdiscal approach has also been described as a safe, equally effective and easier procedure compared to the classic posterior approach [142, 143]. Potential complications of a superior hypogastric plexus block include bleeding, infection, nerve structures and visceral damage and sexual dysfunction [144].

The **ganglion impar**, also known as ganglion of Walther, corresponds to the distal termination of the sympathetic chains as they merge. It is generally located on

the ventral aspect of the sacrococcygeal junction but may lie ventral to the coccyx. It has shown to provide pain relief for patients with pelvic and perineal cancer and effectiveness in treating radiation proctitis pain has been reported [145, 146]. The ganglion impar can be accessed via the anococcygeal ligament, in a midline or paramedian approach; via the sacrococcygeal or intercoccygeal joint spaces or via a lateral approach. A lateral approach seems to reduce the risk of perforating the rectum and avoids needle breakage when bent or inserted through ossified structures [147], but literature is contradictory regarding the best approach.

The appropriate timing for carrying out a neurolytic plexus block should be further investigated but it may be advantageous to perform it before the second step of the WHO analgesic ladder rather than the fourth step [148].

- **Celiac plexus and splanchnic nerves block** is often used to control pancreatic cancer or other upper abdominal malignancies related pain.
- **Superior hypogastric plexus block** enables reduction of pain with lower abdominal or pelvic viscera origin.
- **Ganglion impar block** has shown to provide pain relief for patients with pelvic and perineal cancer and effectiveness in treating radiation proctitis pain has been reported.
- These procedures present important **potential complications**.

## 48.20 Neuraxial Analgesia

Spinal analgesia aim is to achieve high concentrations of opioids and other drugs close to their spinal receptors, thus providing a more effective pain relief than systemic drugs with minimal side effects. It has been estimated that only around 2% of patients receive this kind of analgesia, although 5% or more would benefit from its use [149].

The most commonly used opioid for this purpose is **morphine**, although diamorphine, fentanyl, sufentanil and hydromorphone have also been used [132]. Local anesthetics, such as **bupivacaine**, and **clonidine**, when administered along with opioids, may have a synergistic effect, enabling the use lower opioid doses and, consequently, reducing adverse effects. **Ketamine** in rapid dose escalation (up to 500 mg) in addition to serious adverse events does not appear to have any clinical benefit [150].

Neuraxial analgesia may be **delivered by the epidural or by the intrathecal route**. An epidural analgesia may be preferable when a focal analgesia is aimed,

achieved by placing the catheter tip close to the target location. Besides, it is recommended for the heavily opioid intolerant patient who requires high drug doses delivery. The intrathecal route, on the other hand, is indicated for diffuse pain or for those patients whose epidural space is obliterated by the disease itself or by surgery [149]. Differences between intrathecal and epidural analgesia complications do not appear to be significant, but epidural catheter positioning may be easier at the cervical and thoracic levels [151].

Neuraxial infusions may utilize an **external or implanted system**, being performed by using one of three methods: a percutaneous catheter tunnelled subcutaneously and attached to an external pump; a subcutaneous catheter with an injection port and an external pump; and a subcutaneous catheter and implanted pump. This last option is recommended when patient life expectancy is greater than 3 months – although expensive, this approach becomes cost-effective once treatment duration becomes longer than 3 months. On the contrary, if prognosis is less than 3 months, a tunnelled catheter is usually preferred [151].

Raised intracranial pressure is an absolute **contraindication** to neuraxial analgesia and this technique should also be avoided in the presence of brain metastases due to the risk of herniation and haemorrhage. Local or systemic infection is also impeditive since its spread to the central nervous system may occur. Chronic use of anticoagulants does not contraindicate neuraxial analgesia and it may also be carried out in thrombocytopenic patients although, in this case, platelet transfusion may be considered before catheter insertion [152].

Despite reducing systemic analgesic-related side effects, neuraxial analgesia may also give rise to drug-related or procedure-related **complications**. Intrathecal opioids may produce sedation and respiratory depression since they may reach opioid receptors in the brain, by spreading rostrally in the cerebrospinal fluid. This may be avoided by administering lipophilic opioids as close to the target spinal levels as possible. Practice guidelines have been established to avoid and reverse this respiratory depression [153]. Other opioids side-effects are roughly similar to those occurring in systemic administration and have already been discussed. Intrathecal infusions of local anaesthetics or clonidine may result in hypotension. It should be stressed that cancer patients with a low intravascular volume are particularly vulnerable to this effect [152].

Nerve injury and paralysis are rare and may occur as a result from direct injury to the spinal cord, bleeding and epidural hematoma formation. Postdural puncture headaches are more frequent but, in most cases, they are self-limiting. For the remaining patients, autologous epidural blood patch or fibrin glue may be used. Local infections and meningitis, although rare, can determine catheter removal. Towards the end of life, an adequate pain control may be a priority and maintaining the catheter in place while intrathecal or systemic antibiotics are given can be an appropriate option [132]. 2011 consensus based guidelines recommend surgical site infection prophylaxis [154].

- Spinal analgesia provides high concentrations of opioids and other drugs close to their spinal receptors, thus providing effective analgesia with minimal side effects.
- **Morphine, bupivacaine, and clonidine** are the main drugs used for neuraxial analgesia and may be combined for a synergistic action.
- An **epidural analgesia** may be preferable when a focal analgesia is aimed.
- The **intrathecal route** is indicated for a more diffuse pain or whenever the epidural space is obliterated by the disease itself or by surgery.
- Neuraxial infusions may utilize an **external or implanted system**. A fully implanted system is recommended when patient life expectancy is greater than 3 months.
- Raised intracranial pressure is an **absolute contraindication** to neuraxial analgesia and this technique should also be avoided in the presence of brain metastases.
- Intrathecal opioids may produce **sedation and respiratory depression** since they may reach opioid receptors in the brain, by spreading rostrally in the cerebrospinal fluid.
- **Nerve injury and paralysis** are rare complications of spinal analgesia. **Postdural puncture headache** is more common but is usually self-limiting.

### ***48.20.1 Percutaneous Kyphoplasty and Vertebroplasty***

Vertebroplasty and kyphoplasty are vertebral augmentation procedures consisting of an injection of bone cement into the cancellous or spongy bone of the vertebral body to alleviate pain caused by a vertebral compression fracture. In kyphoplasty, a modification of vertebroplasty, a balloon is previously inserted and inflated in order to create a cavity and only then the bone cement is injected. There is no clear evidence indicating that one of the procedures is superior to the other [155].

**Contraindications** for these procedures include overt instability, cord compression with clinical myelopathy, infection at the fracture site, bleeding disorders and low platelet count. When cord compression is present without neurological symptoms, neuro-monitoring or local anaesthesia with an anterior delivery of cement is advisable [155].

Serious complications are rare with polymethyl methacrylate extravasation being the most common. However, it is asymptomatic and is less frequent in kyphoplasty [155].

## **48.21 Conclusions**

In spite of many technical and pharmacological advances, cancer pain remains a major cause of suffering resulting in poor quality of life for the patients. Cancer pain management presents many difficulties such as lack of pain assessment and



education in opioids prescription including fear of side effects. New medications and invasive techniques may increase pain relief for cancer patients. However, the healthcare provider should always have in mind the complexity of the total pain to find the better approach of its different dimensions contributing not only to the relief of pain, but also allowing exceedingly better quality of life to the patients consequently reducing healthcare and socio-economic burdens.

### Questions

1. Chronic pain can be defined as:
  - (a) a multidimensional experience including physical and psychological aspects
  - (b) a symptom that negatively interferes with subject's role in society
  - (c) a manifestation that negatively affects quality of life
  - (d) a symptom that decreased the ability to cope with cancer
  - (e) all answers are correct
2. The only factor that does not contribute to generate/maintain chronic pain is:
  - (a) endorphins
  - (b) prostaglandins
  - (c) bradykinins
  - (d) endothelin
  - (e) neurotrophic factors secreted by cancer cells
3. Pain must be assessed:
  - (a) only and always with the Numerical Pain Rating Scale
  - (b) only and always with the Faces Pain Rating Scale
  - (c) regularly and individualized according to the patient
  - (d) never with scales or questionnaires
  - (e) only and always with the Brief Pain Inventory
4. The following statements are related to cancer pain treatment major goals, except the:
  - (a) optimize pain control
  - (b) increase in the pharmacologic side effects
  - (c) improve quality of life
  - (d) improve psychological aspects
  - (e) improve function
5. It is true for cancer-related pain management:
  - (a) pharmacologic analgesics, mainly NSAIDs, are the mainstay of cancer pain management
  - (b) opioids present no side effects in cancer pain patients
  - (c) tricyclic antidepressants are the first choice
  - (d) opioids are very effective and well tolerated
  - (e) there is no need for psychosocial support in any cancer pain patient

6. For Opioid-Naïve patients the mild pain treatment should:
  - (a) begin with fast titration of short-acting opioids
  - (b) be only with psychosocial support
  - (c) be with placebos
  - (d) begin treatment with nonopioid analgesics such as NSAIDs and/or acetaminophen, unless contraindicated
  - (e) be with associations of NSAIDs, acetaminophen, weak and strong opioids
7. About the morphine, the wrong affirmation is:
  - (a) is considered the opioid of first choice
  - (b) should be used in high doses for patients with renal impairment
  - (c) can be delivered in multiple formulations and routes, including oral (preferable), parenteral or rectal
  - (d) when converting from oral to parenteral morphine, the equivalent dose is one-third of that of the oral medication
  - (e) only a small percentage of patients are unable to tolerate oral formulas
8. About the methadone, the wrong affirmation is:
  - (a) presents agonist action on opioid and NMDA receptors
  - (b) should be slowly titrated
  - (c) has similar analgesic efficacy and tolerability to morphine
  - (d) should be started at doses lower than those calculated
  - (e) presents inter-individual variation in pharmacokinetics
9. About the tramadol, the wrong affirmation is:
  - (a) is indicated for treating mild to moderate pain
  - (b) is less potent than other opioids
  - (c) should be used in association with tricyclic antidepressants
  - (d) maximum daily dose is 400 mg for adult cancer patients
  - (e) should be avoided in patients taking selective serotonin reuptake inhibitors
10. It is wrong to think that if the cancer pain is severe, unchanged or increased:
  - (a) comprehensive reassessment must be performed with adjustment of the therapeutic plan
  - (b) dose escalation of the current opioid is a common option
  - (c) adjuvant analgesics should be considered
  - (d) physical activity, such as running, should be considered
  - (e) nonpharmacologic integrative interventions should be considered
11. These are possible opioid adverse effects, except:
  - (a) hypertrichosis
  - (b) nausea
  - (c) pruritus

- (d) respiratory depression
  - (e) constipation
12. About opioid related sleep disturbances it is false:
- (a) the base disease could be the main cause
  - (b) opioids could interfere in neurotransmitters balance including serotonin, noradrenalin or dopamine
  - (c) the optimal treatment is to immediately interrupt opioid treatment
  - (d) long-term opioid therapy can cause sleep-disordered breathing syndrome
  - (e) morphine is thought to reduce REM sleep through GABAergic signaling modulation
13. About tolerance to opioids it is false to assume that:
- (a) is defined as the requirement of increased doses to maintain the same analgesic effect
  - (b) cross tolerance is the development of tolerance between oral and IV routes
  - (c) tolerance can be innate
  - (d) acute opioid administration can be related to tolerance development
  - (e) tolerance may also develop to side effects
14. The wrong affirmation about bone pain is:
- (a) initially presents as dull but gradually grows in intensity
  - (b) surgical treatment by osteotomy is the first treatment choice
  - (c) bisphosphonates may have a beneficial effect on metastatic bone pain
  - (d) breakthrough pain may emerge due to cancer extension
  - (e) bone pain is a consequence of neurochemicals released by tumour cells
15. The wrong affirmation about cancer-related neuropathic pain is:
- (a) results from damage to the somatosensory nervous system caused by the disease itself or from its treatment
  - (b) decreases quality of life
  - (c) it usually presents as a background pain with triggered or spontaneous exacerbations
  - (d) it is easy to control
  - (e) the affected areas may be afflicted by hyposensitivity, hypersensitivity or both

### Answers

1e, 2a, 3c, 4b, 5d, 6d, 7b, 8a, 9c, 10d, 11a, 12c, 13b, 14b, 15d

### Commentaries

1. Chronic cancer pain is a multidimensional experience that includes not only physical and psychological aspects but, for the general population, those symptoms negatively interfere with subject's quality of life, including role in family, society, among others, consequently decreasing the ability to cope with cancer.

2. Endorphins are potent analgesic endogenous opioid neuropeptides that relieve pain.
3. Since pain is a multidimensional complex experience, it must be carefully assessed, with regularity due to the fluctuation in time and individualized since it varies between subjects.
4. Cancer pain treatment includes not only the physical symptom, however due to its multidimensionality, the healthcare professional must find tools to optimize pain control, improving function with positive consequences in the patient's quality of life and psychological aspects.
5. Opioids, when properly used, after a careful screening of the patient, are very effective and well tolerated in cancer-related pain management. Analgesic relief and the side effects must be assessed regularly in order to adjust the best therapy.
6. For Opioid-Naïve patients the mild pain treatment should begin with nonopioid analgesics such as NSAIDs and/or acetaminophen, unless contraindicated in order to verify if the weak analgesics are enough to relieve the pain avoiding the risks of strong analgesics.
7. Morphine is considered the opioid of first choice because it can be delivered in multiple formulations and routes, including oral (preferable), parenteral or rectal and only a small percentage of patients are unable to tolerate oral formulas.
8. Methadone, as other opioids, should be individualized, slowly titrated, starting at doses lower than those calculated and presents similar analgesic efficacy and tolerability to morphine. The disadvantage is that this opioid presents inter-individual variation in pharmacokinetics.
9. Tramadol is typically indicated for treating mild to moderate pain being less potent than other opioids. The maximum daily dose is 400 mg for adult cancer patients and should be avoided in patients taking selective serotonin reuptake inhibitors.
10. When cancer pain is severe, unchanged or increased, a comprehensive reassessment must be performed with adjustment of the therapeutic plan by dose escalation of the current opioid together with the adjuvant analgesics and nonpharmacologic integrative interventions, when the adjustment is not sufficient.
11. The typical opioid adverse effects are nausea, pruritus, respiratory depression and constipation. Respiratory depression, despite not common, is the most feared side effect.
12. Opioid therapy should never be immediately interrupted, but reduced or replaced, due to the withdrawal syndrome.
13. Cross tolerance is when opioid promotes the development of tolerance to another drug.
14. Surgical treatment by osteotomy will not promote analgesic effects since it will only jeopardize the bone and adjacent tissues, probably generating more pain.
15. Cancer-related neuropathic pain is very difficult to manage as any neuropathic pain since the damage to the somatosensory nervous system is very hard to revert.

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# Chapter 49

## Bone Metastasis



**Arlindo R. Ferreira, André N. Abrunhosa-Branquinho, Marília Jorge, and Luís Costa**

**Abstract** Bone is a common site of distant involvement in advanced cancers. About 70% of patients with advanced breast and prostate cancers and up to 30–40% of patients with advanced lung, thyroid and kidney cancers develop metastatic bone disease.

Cancer-bone cell interactions are complex and can lead to altered bone metabolism and increased bone fragility. Metastatic bone disease is associated with significant morbidity and can have a substantial survival impact. Typically, skeletal complications of bone metastasis include pathological fracture, spinal cord compression, the need for surgery or radiotherapy for a symptomatic bone metastases, and hypercalcemia, collectively referred as skeletal-related events (SREs).

The treatment landscape of bone metastasis is multimodal and has evolved over the last decade. It includes both medical, radiation and surgical management.

In this chapter we will review the epidemiology, pathophysiology, clinical evaluation and management of metastatic bone disease from solid tumors.

**Keywords** Bone metastasis · Solid tumors · Bone-targeted agents

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## Abbreviations

ALP	Alkaline phosphatase
BMPs	Bone morphogenetic proteins
BP	Bisphosphonate
BS	Bone scintigraphy
BTA	Bone-targeted agents
CRT	Conventional radiotherapy
CT	Computerized tomography
CXCL12	C-X-C motif chemokine 12
CXCR4	C-X-C chemokine receptor type 4
CXCR7	C-X-C chemokine receptor type 7
IGF	Insulin like growth factor
IL	Interleukin
ISUP	International Society of Urological Pathology
IV	Intravenous
LHRH	Luteinizing hormone releasing hormone
MRI	Magnetic resonance imaging
NTX	N-terminal cross-linked telopeptide of type I collagen
PET	Positron emission tomography
PO	<i>Per Os</i>
PTHrp	Parathyroid hormone-related peptide
RANKL	Receptor activator of nuclear factor $\kappa$ B ligand
RT	Radiotherapy
SBRT	Stereotactic Body Radiotherapy
SC	Subcutaneous
SRE	Skeletal related event
TGF- $\beta$	Transforming growth factor- $\beta$
TNF- $\alpha$	Tumor necrosis factor $\alpha$
XR	Plain radiograph
ZA	Zoledronic acid

### 49.1 Introduction

Bone metastases are a significant hazard for patients with cancer, with differences by cancer type. In this chapter we will review the epidemiology, pathophysiology, clinical evaluation and management of metastatic bone disease from solid tumors.

### 49.2 Epidemiology

Patients with prostate and breast cancers are the most commonly affected by bone metastasis, with 5-year incidence of 17% and 5%, respectively, and, among patients with advanced cancer, a prevalence of 90% and 70%, respectively [1–4]. For patients

with advanced lung, thyroid and kidney cancers, bone involvement is reported in up to 30–40% of the cases [5]. In the other extreme, patients with gastro-intestinal tract tumors only rarely have bone metastatic disease [5]. This heterogeneous incidence and prevalence is driven by differences in bone tropism, both due to anatomic characteristics (such as blood drainage of the breasts following the Batson venous plexus), but also related with intrinsic biologic and molecular features [6, 7].

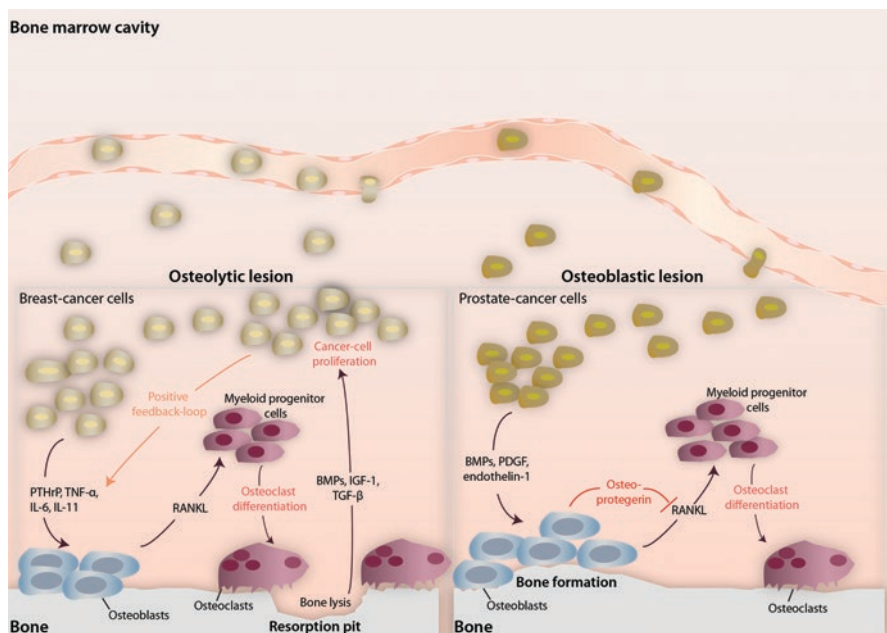
Regardless of the primary cancer, bone involvement has the potential to significantly negatively impact patients' quality of life metrics and/or survival, as well as to increase health care resources consumption [8]. This is mostly due to adverse bone outcomes, collectively referred as skeletal related events (SRE; pathological fracture, spinal cord compression, the need for surgery or radiotherapy for symptomatic bone metastasis and hypercalcemia of malignancy). In a population-based study, the 3-years incidence rate of pathological fracture, spinal cord compression and the need for surgery or radiotherapy for symptomatic bone metastasis was 211 per 1000 patients for breast cancer, 260 per 1000 patients for lung cancer and 150 per 1000 patients for prostate cancer, with the incidence of hospital admissions due to bone metastases ranging from 95 per 1000 for breast cancer, 156 per 1000 for lung cancer and 163 per 1000 for prostate cancer [9].

### 49.3 Molecular Mechanisms

The interaction between cancer cells and bone is a complex and incompletely understood process. Chemoattractant factors released from the bone marrow, such as CXCL12, contribute partially for the tropism of cancer cells to the bone; tumor expression of chemokine receptors, specifically CXCR4 and CXCR7, interact with the bone chemoattractant stimulus CXCL12 and induce bone homing [6, 10]. The process is further completed with the adhesion of tumor cells to the bone matrix through, e.g., the expression of integrins, such as  $\alpha 4\beta 1$  or  $\alpha 2\beta 1$  [6].

Bone is under permanent remodeling through the coupled activity of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells). Cancer cells disturb bone turnover equilibrium by affecting bone cells and benefiting from the release of agents entrapped in the bone matrix. These agents enhance tumor growth and lead to increased bone fragility [11, 12]. An interdependent cycle of a) bone turnover activation by tumor cells and b) tumor cell growth stimulation by factors entrapped in the bone matrix is established, thus generating a positive reinforcement loop known as the vicious cycle [13].

When in the bone, cancer cells activate osteoblasts through the release of parathyroid hormone-related peptide (PTHrp), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin 1 (IL-1), IL-6, IL-8 and IL-11 [14]. Activated osteoblasts produce receptor activator of nuclear factor  $\kappa$  B ligand (RANKL) that ultimately activates osteoclasts and hence induces bone resorption [14]. Finally, growth factors entrapped in the bone matrix, such as transforming growth factor- $\beta$  (TGF- $\beta$ ), bone morphogenetic proteins (BMPs), insulin like growth factor (IGF) and fibroblast growth factor are released inducing tumor growth [15]. The sum of these steps allows the generation of the previous referred self-perpetuating cycle known as the vicious cycle (Fig. 49.1).



**Fig. 49.1** Interactions between bone and cancer cells in paradigmatic examples of osteolytic (breast cancer) and osteoblastic (prostate cancer) bone metastases. In both examples bone metabolism with resorption and formation occurs. The depicted mediators emphasize the predominant pathways

## 49.4 Diagnosis

### 49.4.1 Clinical Findings

Metastatic bone disease affects more commonly the axial skeleton (pelvis, spine and ribs) and femurs. Approximately one third of the bone lesions are asymptomatic [16]. When symptoms are present, pain is the most common (50%) [17]. In addition to pain, bone fracture, spinal cord compression, hypercalcemia of malignancy and the need for surgery/radiotherapy for the management of symptomatic bone metastases, frequently referred as SREs, are also a common manifestation of metastatic bone disease, more often in patients with lytic disease [8].

### 49.4.2 Laboratory Findings

Alkaline phosphatase (ALP; a marker of bone formation) and N-terminal cross-linked telopeptide of type I collagen (NTX; a marker of bone degradation) are commonly elevated in patients with bone metastases. Although informative, neither of these markers are recommended to guide clinical decisions [18].

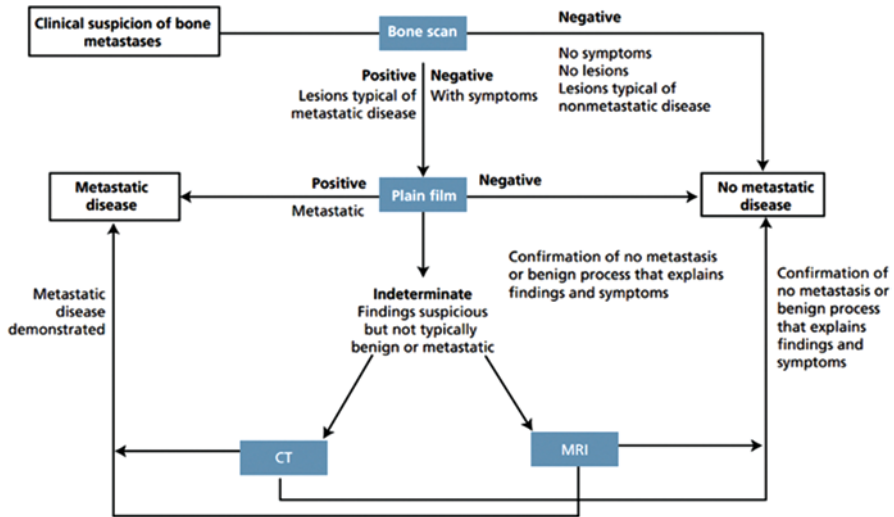


Fig. 49.2 Algorithm for imagological evaluation of patients with clinical suspicion of bone metastases. (Adapted from Ref. [19])

### 49.4.3 Radiologic Assessment

The radiologic assessment of metastatic bone disease can involve different imaging options, which provide complementary information (see diagnostic algorithm in Fig. 49.2). These include plain radiographs (XR), bone scintigraphy (BS), computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan. Usually, when metastatic bone disease is suspected, BS and XR are the first exams to be requested. XR is widely available and is relatively inexpensive. However, 30–75% of normal bone mineralization must be degraded before osteolytic findings in the lumbar vertebrae become apparent on XR, delaying the diagnosis of metastatic lesions for several months [19]. BS is more sensitive than XR for the diagnosis of metastatic bone disease (62–100% vs. 44–50%). However, BS has lower specificity and therefore a higher false-positive rate. BS findings reflect the osteoblastic activity and skeletal vascularity (not the tumor cells themselves), therefore other bone insults, such as trauma or inflammation, can lead to false positive results. On the other hand, rapidly growing pure osteolytic metastasis, when bone turnover is slow, or when the site is avascular can lead to false-negative results. In clinical practice, XR and BS are complementary methods, with XR helping to clarify nonspecific or atypical findings.

CT scans and MRI are usually used to further characterize bone disease. CT scan is very sensitive when detecting small cortical erosions and fractures (71–100%) [19]. Bone MRI has a reported sensitivity of 82–100% and specificity from 73% to 100% for the diagnosis of bone metastasis. MRI is commonly used to assess pathologic fractures of the hip and pelvis, as well as spinal cord compression [20].



Finally, the emergence of PET scan, and particularly of the combination of PET scan with CT (PET/CT) led to a more widespread use of this method as an option to evaluate bone disease. Nevertheless, PET without the CT component is not an ideal method for the diagnosis of osteoblastic lesions [21]. While for most tumors  $^{18}\text{F}$ -fluorodeoxyglucose is the label of choice for PET/CT, for prostate cancer  $^{11}\text{C}$ -choline and  $^{68}\text{Ga}$ -PSMA were more recently established as the preferred labels [22].

#### ***49.4.4 Longitudinal Assessment of Bone Disease***

The longitudinal assessment of bone disease is challenging. In fact, the Response Evaluation Criteria in Solid Tumors (RECIST) only considers bone lesions as “measurable” if associated to a soft tissue component  $\geq 10$  mm. To overcome RECIST limitations, bone-specific (MD Anderson [MDA]) and metabolic-specific (Positron Emission Tomography Response Criteria in Solid Tumors [PERCIST]) response criteria were developed, however the uptake of these criteria has been minor. In prostate cancer, the Prostate Cancer Clinical Trials Working Group (PCWG) developed guidelines to standardize disease assessment, also when affecting the bone [23]. Overall, a combination of clinical symptoms, laboratory findings and imaging data is necessary to interpret bone disease.

### **49.5 Treatment Approaches**

The treatment goals of metastatic bone disease are symptoms control, as well as the improvement in quality of life and survival. Both systemic (anti-tumor and bone targeted agents) and local treatments (radiotherapy and surgery) are available. These approaches may be used sequentially or in combination.

#### ***49.5.1 Systemic Management***

The systemic management of metastatic bone disease has evolved over the last decade to include therapies directed to the tumor and bone environment.

1. Tumor directed therapy
  - 1.1. Medical management

Tumor directed therapies (chemotherapy, hormonal therapy and biologics) are useful for the management of metastatic disease in tumors known to respond to these modalities. Tumor directed therapy should follow the appropriate metastatic

treatment guidelines for each primary tumor. Cancer medullar involvement and chemotherapy can induce an additive hematologic toxicity.

## 1.2. Bone-targeted radioisotopes

Bone-targeted radioisotopes are a group of bone-seeking radioactive elements that emit  $\alpha$  or  $\beta$  radiation. Examples of such agents include radium-223, strontium-89 and samarium-153 [24]. Despite their theoretical applicability to a broad range of tumors, current clinical use is mostly restricted to radium-223 (an  $\alpha$  particles emitting radioisotope) in adults with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases. This label of radium-223 was obtained after the results of the pivotal ALSYMPCA study, a phase III trial of Radium-223 against placebo in 921 patients with castration-resistant prostate cancer and bone metastases that were not eligible or refused docetaxel. In this study, radium-223 extended survival (14.0 vs. 11.2 months; HR 0.70; 95% CI 0.55–0.88,  $p = 0.002$ ) and time to first symptomatic SRE (15.6 months vs. 9.8 months) [25]. No other radiopharmaceuticals showed a survival impact in the management of solid tumors with bone metastases, but methodological limitations might limit the interpretation of those studies [24].

## 2. Bone targeted agents (BTA)

Bisphosphonates (BP) and denosumab are the two class of drugs approved for the prevention of SREs in patients with advanced malignancies affecting the bone. As of January 2019, denosumab is indicated for solid tumors and multiple myeloma both in the EU and in the US.

### 2.1. Available BTAs, Administration and Efficacy

Bisphosphonates are incorporated in the bone matrix and absorbed by osteoclasts during bone remodeling. Inside osteoclasts, BPs block the osteoclast activity and ultimately bone resorption, thus, in patients with bone metastases, BPs halt the vicious cycle of bone metastases and the rate of SREs. BPs are a class of agents that include, among others, zoledronic acid (4 mg IV over 15 min every 3–4 weeks), and ibandronate (50 mg PO daily).

Pamidronate (another BP) was compared to placebo showing an improvement in skeletal morbidity rate and median time to SRE (12.7 vs 7 months,  $P < 0.001$ ) [26]. Pamidronate was subsequently compared to ZA in a phase III study involving 1648 patients with bone metastases from breast cancer and multiple myeloma that showed a 16% reduction in the overall risk of SREs in those treated with ZA and with a similar safety profile [27]. Favorable results for ZA were also reported for patients with castration-resistant prostate cancer (36% reduction of SREs risk when compared to placebo), lung (31% reduction of SREs risk when compared to placebo) and renal cell (58% reduction of SREs risk when compared to placebo) cancers [28, 29]. A weaker but clinical significant evidence of efficacy was also documented for other solid tumors, as thyroid and bladder cancer [28]. Oral formulations of BPs, as ibandronate, are also available. These formulations, despite less efficacious in terms of skeletal morbidity, have a comparable safety profile and for some patients are

viewed as having a more convenient mode of administration [30]. In this setting, no overall survival differences were found. Therefore, oral options can be discussed with the patient if a strong preference is present or if difficulties with intravenous formulations occur.

Denosumab is a fully human monoclonal antibody with high affinity for RANKL. The interaction between denosumab and RANKL decreases the availability of RANKL, thus blocking its natural interaction with the osteoclast precursor surface receptor RANK and precluding osteoclast formation, bone resorption, and in patients with bone metastases SREs.

Denosumab (120 mg SC every 4 weeks) was compared to ZA in a phase III trial including 2046 patients with bone metastases from breast cancer [31]. Denosumab was superior in delaying time to first on-study SRE (26.4 months vs not reached;  $P = 0.01$  for superiority) and time to first and subsequent (multiple) on-study SREs. A similar safety profile was documented. Denosumab has also demonstrated favorable results when compared to ZA in patients with castration-resistant prostate cancer (18% reduction on time to first SRE) [32]. Of note, hypocalcemia was more frequent in prostate cancer patients (13% vs. 6% in ZA group). For patients with other types of solid tumors and multiple myeloma denosumab was non-inferior to zoledronate [33]. A subsequent meta-analysis concluded that denosumab is superior to ZA in the prevention of bone complications from bone metastases, but no effect on survival was found [34]. Furthermore, the cost of denosumab is significantly higher than that of ZA, particularly where generic BPs are available.

This data is summarized in international guidelines that consider denosumab and ZA as equally valid options in the setting of bone metastases [35, 36].

## 2.2. Treatment Duration and Schedule

Pivotal trials have arbitrarily defined treatment duration for bisphosphonates of around 2 years, and for denosumab of up to 3 years. However, there is no rationale to stop BTAs in patients with active bone metastasis. In this setting, international guidelines recommend treatment with BTAs until evidence of substantial decline in patient's general performance status or even indefinitely [35, 36].

Despite the approved scheduling of BTAs, several trials tested the administration of ZA every 12 weeks (instead of every 3–4-weeks) in patients with metastatic breast cancer, as a strategy to decrease treatment toxicity and hospital visits. In a recent meta-analysis, this schedule showed a similar SRE risk when compared to a every 4-weeks administration [37]. Subsequent individual study updates [38, 39], and recent guidelines support this approach [35]. Of note, ZA de-escalation should be done with caution in patients with extra-bone metastases, previous SREs, disease with aggressive behavior and time to BTA introduction  $\geq 6$  months (from the diagnosis of bone metastasis).

## 2.3. Side Effects

Osteonecrosis of the jaw (ONJ) is an uncommon (approximately 1.6% of those receiving ZA or denosumab) but serious side effect from parenteral BTAs [40]. ONJ is a persistent lesion in the oral cavity exposing bone despite adequate treatment for

at least 8 weeks and without local evidence of malignancy nor prior radiotherapy to the affected region [41]. The risk of ONJ increases with prolonged therapy duration (median time to ONJ in patients receiving ZA or denosumab of 15 months) [40]. Patients at higher risk include those with recent invasive dental procedures (extractions or implants), trauma, poor dental hygiene, and therapy with antiangiogenic agents and probably corticosteroids. Every invasive dental procedure should be done several months before treatment with bone modifying agents, and BPs discontinued for 3 months before and after elective invasive dental surgeries. Patients should be encouraged to maintain good oral hygiene and clinicians should assess in every visit jaw/tooth pain or exposed bone on clinical examination. A conservative management is recommended with limited debridement, antibiotics and oral rinses (as chlorhexidine) [41].

Other shared side effects from BTAs include:

1. Hypocalcemia. Patients should be encouraged to take supplemental calcium and vitamin D and serum calcium, magnesium and phosphate monitored during therapy.
2. Acute phase response. This reaction is characterized by fever and flu-like symptoms occurring in the first 3 days after therapy and shortly resolving. Paracetamol or NSAIDs improve symptoms. It generally does not recur after first or second administration.

BPs have specific side effects:

1. Nephrotoxicity. ZA induces tubular dysfunction, while pamidronate damages the glomeruli. Patients should maintain adequate hydration and clinicians need to monitor renal function during therapy. A dose reduction is recommended for patients with creatinine clearance <60 mL/min and BPs are contra-indicated for those with creatinine clearance <30 mL/min.
2. Ocular toxicity. Conjunctivitis, uveitis, scleritis and orbital inflammation were documented.
3. Bone joint or muscular pain.
4. Atypical femoral fractures (subtrochanteric or diaphysis regions) for patients treated for more than 3–5 years.

### **49.5.2 Local Treatments**

The assessment for the best local treatment is based on the lesion localization (axial skeleton vs. extremities), lesion features and patient's fitness. A combination of localized treatments can be proposed (e.g., surgery followed by radiation). The NOMS (Neurological, Oncologic, Mechanical and Systemic) decision framework is recommended as a decision tool in the management of axial/spine metastasis [42]. Other popular decision tool is the Mirels score for femoral lesions: in this system, axial cortical involvement >30 mm and/or circumferential cortical

involvement >50% were significant predictors of bone fracture and thus mandates prophylactic local treatment [43].

## 1. Radiation therapy

RT aims at (1) relieving localized pain, (2) treating spinal cord compression and (3) complementing primary surgical treatment [44, 45]. RT can be combined with other treatment modalities, as e.g. bisphosphonates [46]. Conventional RT (CRT) can relieve pain in 60–80% of cases, with complete pain resolution in 15–30% within 3–4 weeks of treatment [44, 47].

There are different hypofractionated schemes for CRT [44, 48]:

- 30 Gy in 10 fractions/daily (30Gy/10fx),
- 20 Gy in 5 fractions/daily (20Gy/5fx) and
- 8 Gy in a single fraction [8Gy/1fx]).

Different fractionation schemes are determined by patient characteristics, tumor features, symptoms and previous treatments.

### 1.1. Localized non-complicated painful bone metastasis

For non-complicated/“uncomplicated” bone metastasis, defined as the “presence of painful bone metastasis unassociated with impeding or existing pathologic fracture, or presence of spinal cord or cauda equine compression” [49], CRT with 8Gy/1fx is feasible, easy to implement and cost-effective [48, 50]. A systematic review from Chow *et al* showed similar results between a single fraction versus non-single fractionation for pain control (overall pain response rates of 60% vs. 61% with a pooled odds ratio of 0.98 [95% CI 0.95–1.02]; and pain complete response rates of 23% vs. 24% for non-single fractionation with a pooled odds ratio of 0.97 [95% IC 0.89–1.06]) [51]. Another systematic review also failed to show significant differences in efficacy or in toxicity between non-single fractionated CRT schemes [52]. However, single fraction CRT requires re-treatment more frequently (20% vs. 8% for non-single fractionation) with a 2.6-fold higher likelihood for re-irradiation (95% CI 1.92–3.47;  $p < 0.001$ ). In this setting, a minimum interval of 4 weeks between treatments is recommended for re-treatment [44, 48] and up to 2/3 of the patients (95% CI 0.49–0.67) will have pain relief after re-irradiation with CRT [53]. Moreover, similar rates of response to re-irradiation are expected between single and non-single fractionations [52]. The RTOG 0433/NCIC CTG SC 20 trial demonstrated that 8 Gy/1fx for re-irradiation is non-inferior and less toxic than 20 Gy/5fx [54].

A special attention should be given for patients with bone pain with neuropathic features. In these cases, beyond palliative radiotherapy, drugs known to be effective in neuropathic pain (e.g., gabapentin and opiates) should also be prescribed [55, 56]. Moreover, the use of single fractionation CRT is debatable, as highlighted by the TROG 96.05 results that favored the 20Gy/5fx scheme when compared with the 8Gy/1fx [57]. In specific, the 20Gy/5fx scheme had a trend for better overall response rate (61% vs. 53%), complete response rate (27% vs. 26%) and less consumption of analgesics and hospital admission costs.

### 1.2. Radiotherapy options in impending bone fracture, bone fracture and in the postoperative setting

For impending or pathological fractures, surgery should be the first approach when possible. There is no recommendation for fractionation or radiotherapy technique to treat an unstable spine, and isolated RT should be avoided whenever possible [58]. The same should be applied for appendicular bones with impending fracture.

In the postoperative setting, metallic prosthesis and surgical hardware are not an absolute contraindication for radiation, but they can interfere with RT planning as imaging artifacts affect delineation and metal alters dosimetry planning. Therefore, unnecessary metal instruments on the patient's skin (e.g., staples) during the planning-CT scan should be avoided. RT should start within 2–3 weeks after surgery [59].

One of the pivotal studies of postoperative CRT included patients with spinal bone metastasis and initial signs of spinal cord compression [60]. In this study, patients were treated with surgery plus 30G/10fx starting within 15 days after surgery. Ability to walk, the study primary endpoint, was more frequent in the postoperative RT group (84% vs 57% in the RT only group; odds ratio 6.2, 95% CI 2.0–19.8;  $p = 0.001$ ). Of note, this trial was performed before recent improvements in the systemic treatment for many tumors, and the advent of increasing aggressive management of oligometastasis. This further highlights the need for improved local control of bone metastasis in patients with increasing survival. In case of recurrent spinal compression, pre-treatment neurological status is an important decision and prognostic factor. Expert consensus suggests surgical decompression due to higher salvage rates, despite foreseeable complications [61].

In case of patients with appendicular bone lesions eligible for surgery, postoperative CRT is frequently used (either 30Gy/10fx or 20Gy/5fx). This is especially valid for long bone lesions, to promote bone remineralization, and to decrease the likelihood of second surgery, re-irradiation, tumor progression and/or prosthesis displacement [62]. Unfortunately, prospective evidence is lacking, and current approaches are based on retrospective data that disregards recent treatment innovations [63].

For the management of spinal cord compression, please refer to the corresponding chapter.

### 1.3. Toxicity associated with radiotherapy

Some of the acute side effects of CRT include [48, 64–68]:

- Fatigue, the most frequent side effect (80–90%).
- Pain flare, a sudden increase from basal pain within a week after the start of the treatment. It is identified up to 3–44% cases and it lasts for a median of 3 days.
- Acute gastrointestinal and hematological toxicities are expected on large radiation volumes. Prophylactic oral anti-emetics should be given and blood counts should be monitored.
- Pathological fractures are less frequent but can occur in stereotactic body radiotherapy (SBRT) (<10%) and data is still equivocal for single fraction CRT.

- Spinal cord injury risk is <0.2% with CRT technique if constrain dose is respected (maximum dose 50 Gy).

## 2. Surgical management and other invasive procedures

The surgical management of bone metastasis aims to achieve pain relief, skeletal stabilization and the prevention of impending fractures or spinal cord compression [59]. Elective interventions of impending fractures are associated with shorter intra-operative time and blood loss, shorter hospital stay, greater likelihood of discharge to home as opposed to an extended care facility and greater likelihood of resuming support-free ambulation [69].

The selection of patients and type of intervention depends on the estimated life expectancy, the mental and motor status, pain control and general nutritional and metabolic status [59]. Relative contraindications for surgery are related to patient fitness, expected overall survival to benefit from the surgical treatment (ranging from 1 to 3 months), extensive neurovascular enclosure by tumor extension, malnutrition (which would preclude wound healing) and metastasis in other sites compromising function.

Major surgery complications include peri-operative death (from 6% to 15%), fixation failure, infection and thromboembolism [70].

### 2.1. Disease of the extremities

Femoral lesions are the most common lesions of the extremities. Surgery can be directed to (1) impending fractures or (2) established pathologic fractures. Commonly used surgical approaches in lesions of the extremities include bone reinforcement with or without removal of metastasis, reconstruction of the articular surface or amputation.

- (1) The selection of patients with impending fractures is assessed by various scores, as, e.g. Harrington or Mirels score systems. Prophylactic surgery usually involves internal fixation followed by RT.
- (2) Pathologic fractures of long bones diaphysis (femur or humerus) are usually treated with internal fixation with bone cement and interlocking screws followed by RT. Femoral head and neck fractures are better treated with hemiarthroplasty. Surgical techniques for femur intertrochanteric, subtrochanteric and acetabular lesions as other bone site lesions are out of this chapter scope.

### 2.2. Disease of the axial skeleton

Indication for surgical intervention should be based on the NOMS decision framework and expected functional impairment after treatments. As a rule of thumb common indications include the presence of spinal instability, neurological deficit or functionally relevant deformity. Surgery is also indicated in symptomatic lesions from tumors that are radioresistant (e.g. renal cell carcinoma) or that continue to progress despite RT.

Common approaches to axial lesions include surgical anterior/posterolateral decompression with vertebrectomy and graft or cage reconstruction; laminectomy;

and percutaneous vertebroplasty or balloon kyphoplasty, both of which include de intra-vertebral injection of methyl methacrylate cement. Adjuvant RT and orthosis, as cervical/spinal collars, are frequently used.

## 49.6 Future Developments

Several points in the treatment of bone metastases are under active research. In prostate cancer, these include treatment combinations of the radiopharmaceutical radium-223 with other direct antitumor agents as abiraterone, enzalutamide, or docetaxel. To this regard, the randomized, double-blinded phase III ERA-223 trial (NCT02043678) of abiraterone plus prednisone with either radium-223 or placebo in chemotherapy-naive patients with asymptomatic or mildly symptomatic mCRPC with bone metastases was prematurely stopped due to the identification of more fractures and deaths in the combination arm.

At the same time, several studies are moving BTAs from the palliative setting to the adjuvant setting. To this end, ZA has already shown to be useful for the prevention of bone metastases in postmenopausal women with early breast cancer treated with curative intent. In the genomic era, several groups are also seeking to define gene signatures predicting for the risk of development of bone metastases. In addition, active research is also looking for the development of new classes of BTA.

In the CRT field, the Post-operative RadioTherapy for Patients With Metastases of the Long Bones (PORT) trial (NCT02705183) will update the evidence of delivering postoperative CRT to impending and pathological fractures.

Growing evidence supports the use of Stereotactic Body Radiotherapy (SBRT) as an ablative treatment for localized bone metastasis, while maintaining spinal cord dose constraints. Available data tested its use in fit patients with limited metastasis (oligometastatic) and expected to survive longer than 3–6 months. Other indications might include recurrent bone lesions after CRT, irradiation of radioresistant tumors and as a complementary post-operative treatment [58]. Expert consensus have been developed to standardize treatment and to define standards for the collection of outcomes for non-irradiated, previously irradiated and for complementary postoperative RT. [71, 72]

### Key Points

- Bone metastases are a significant hazard for patients with cancer, especially in patients with prostate and breast cancers;
- The axial skeleton (pelvis, spine and ribs) and femurs are the most frequently affected sites and pain the most common symptom (50%) with a third of patients being asymptomatic;
- Bone targeted agents (as bisphosphonates and denosumab) are effective treatments to reduce the incidence of skeletal related events, a group of bone complications including pain, fracture, spinal cord compression, hypercalcemia of malignancy and the need for surgery/radiotherapy for the management of symptomatic bone metastases;



- RT is used to relieve localized pain, treat spinal cord compression and as a complementary treatment after surgery; for patients with uncomplicated bone metastasis, CRT in a single fraction of 8 Gy is non-inferior to other non-single fractionated schemes.
- In case of unstable spine or neurological impairment, surgery should be the first approach when possible.

### Clinical Case

An 80 years-old male, previously independent, was admitted to the emergency room with pain in the right thigh. Patient had medical history of osteoarthritis affecting both hips and recently developed constipation, unusual generalized weakness and nausea, but could still performed his daily routine. Laboratory workup revealed an elevated ALP, hypercalcemia (13.5 mg/dL), no renal injury and an elevated PSA (172 ng/mL). A bone XR and subsequent CT scan revealed a low density lesion involving all circumference of the right femur diaphysis, thus compatible with impending bone fracture. Patient was given analgesia and electrolytes were optimized. Afterwards, patient was submitted to orthopedic surgery with lesion removal, internal fixation and interlocking screw placement. Subsequent external radiotherapy was administered (20 Gy in 5 fractions). Pathological review confirmed prostate adenocarcinoma. Additional clinicopathological workup revealed a prostate adenocarcinoma, Gleason Score 8 (4+4)/ISUP grade group 4, T3b, with lumbar and right femoral bone metastasis but no visceral involvement. Patient was discussed at the urological tumor board and subsequently started on androgen deprivation therapy with an LHRH antagonist. Given the castration sensitive setting, he was not started on bone targeted agents.

### Multiple-Choice Questions

1. Bone metastases are a systemic complication of solid tumors. Select the false:
  - (a) Tumor cells reach the bone through a combination of mechanisms, including biochemical homing and anatomical characteristics of the primary;
  - (b) The vicious cycle of bone metastases explains the mechanism by which tumor cells manipulate and derive benefit from the bone microenvironment;
  - (c) In the vicious cycle of bone metastases, PTHrp is released by cancer cells to activate osteoblasts that subsequently produce RANK ligand that ultimately activates osteoclasts and hence induce bone resorption and the release of growth factors entrapped in the bone matrix;
  - (d) The 3 tumors with the highest likelihood of metastization to the bone are prostate, breast and colon cancers;
  - (e) Typical growth factors released by the bone matrix include TGF-  $\beta$ , BMP, IGF and FGF.

**Correct answer:** d

**Comments:** While patients with prostate, breast cancers, lung, thyroid and kidney cancers develop frequently bone metastases, those with gastro-intestinal cancers, as colon cancer, develop less frequently bone metastases.

## 2. Regarding clinical presentation of bone metastases:

- (a) Large bones, as e.g. the humerus, are the most commonly affected sites;
- (b) More than half of patients show no symptoms at presentation;
- (c) The N-terminal cross-linked telopeptide of type I collagen is a biochemical mediator of pain;
- (d) X-ray and bone scintigraphy are complementary imaging methods, with X-ray helping to clarify nonspecific or atypical findings of bone scintigraphy
- (e) MRI is better than CT-scan in detecting cortical bone erosion

**Correct answer: d**

**Comments:** Bone scintigraphy (BS) is more sensitive than X-ray for the diagnosis of metastatic bone disease, but BS has lower specificity, given that other bone insults, such as trauma or inflammation, can lead to false positive results; conversely, pure osteolytic metastases, when bone turnover is slow, or when the site is avascular can lead to false-negative results. Therefore, X-ray and BS are complementary methods.

## 3. What should be the first approach if you suspect a solitary painful bone metastasis?

- (a) Always request a bone biopsy to assess the nature of lesion;
- (b) Early treatment with surgery showed to universally improve survival;
- (c) Start with upfront denosumab, given that no other bone targeted agent showed to improve survival;
- (d) Request a bone MRI, given its superior sensitivity for the diagnosis of bone metastasis;
- (e) Characterize pain and other symptoms, exclude neuropathic pain and neurological impairment, as well as assess fracture risk before deciding next treatment steps.

**Correct answer: e**

**Comments:** the management of a new painful lesion in the bone should focus on characterizing patient's symptoms and risk of skeletal complications in order to act appropriately both in terms of symptoms palliation and avoidance of acute complications, as SREs.

## 4. Regarding the treatment of bone metastases, select the false:

- (a) Treatment goals include symptoms control, improvement in quality of life and extension of survival;
- (b) Combination of treatment options, such as surgery and radiotherapy, are experimental, and should only be performed in the setting of a clinical trial;
- (c) Despite the existence of several bone-targeted radioisotopes, only radium-223 showed to both impact bone outcomes and overall survival in prostate cancer;

- (d) Radium-223 is an  $\alpha$  particles emitting radioisotope, thus presenting less hematologic toxicity;
- (e) Denosumab and bisphosphonates have slightly different approval indications.

**Correct answer:** b

**Comments:** the use of surgery and post-operative radiotherapy is the standard of care both for axial and appendicular lesions. This is based on randomized data for axial lesions, but only retrospective data for appendicular lesions, where most evidence reflects patients with lesions affecting the long bones.

5. Regarding the various options of bone-targeted agents, select the false:
- (a) Denosumab is superior to zoledronic acid in all indications and should always be the preferred option;
  - (b) Bone-targeted agents do not improve survival, but contribute substantially to reduce morbidity;
  - (c) For the majority of patients with breast cancer and bone metastases, the scheduling of zoledronic acid can either be every 3 weeks, every 4 weeks or every 12 weeks;
  - (d) Ibandronate is an oral bisphosphonate and, despite being less efficacious in terms of reducing skeletal morbidity, is still a reasonable alternative in patients with strong preference for oral drugs or if difficulties with intravenous formulations occur.
  - (e) Denosumab is administered subcutaneously.

**Correct answer:** a

**Comments:** denosumab is superior to zoledronic acid (in terms of delaying time to first on-study SRE and time to first and subsequent SREs) in patients with castration resistant prostate cancer and breast cancer. For the remaining types of cancer, denosumab was non-inferior to zoledronic acid. Of note, differences in safety and tolerability profiles should also be taken into consideration.

6. Regarding the various options of bone-targeted agents, select the false:
- (a) Zoledronic acid is a bisphosphonate administered intravenously and no faster than in 15 min;
  - (b) Treatment de-escalation of zoledronic acid for every 12-weeks is a reasonable alternative in all patients with bone metastases, regardless of symptoms, previous SREs and type of primary;
  - (c) Ibandronate is an oral bisphosphonate administered once daily;
  - (d) Denosumab is administered subcutaneously every 4 weeks.

**Correct answer:** b

**Comments:** most evidence around treatment de-escalation of zoledronic acid is available for patients with breast and prostate cancer. Of note, this should be done with caution in patients with extra-bone metastases, previous SREs, disease with aggressive behavior and time to BTA introduction  $\geq 6$  months.

7. Regarding the side effect osteonecrosis of the jaw, select the false:
- (a) Osteonecrosis of the jaw (ONJ) is an uncommon side effect of bone targeted agents occurring in less than 2% of cases;
  - (b) A conservative management is recommended with limited debridement, antibiotics and oral rinses (as chlorhexidine);
  - (c) The risk of ONJ increases with prolonged therapy duration;
  - (d) Invasive dental procedures should be done several months before treatment with bone modifying agents, and BPs discontinued for 3 months before and after elective invasive dental surgeries are performed;
  - (e) Dental hygiene is not related with the risk of ONJ.

**Correct answer:** e

**Comments:** Poor dental hygiene is an established risk factor for ONJ.

8. Side effects of bisphosphonates include all of the following, except:
- (a) Hypocalcemia
  - (b) Flu-like symptoms
  - (c) Minor alopecia
  - (d) Nephrotoxicity
  - (e) Uveitis

**Correct answer:** c

**Comments:** bisphosphonates are not associated with alopecia.

9. What is SRE?
- (a) A type of bone treatment for patients with bone metastases;
  - (b) It is an acronym of typical sites of bone metastases in patients with lung tumors;
  - (c) It is a common composite endpoint of adverse bone outcomes for clinical trials testing drugs targeting bone metastases and stands for skeletal-related events;
  - (d) It is a special radiotherapy technique for the treatment of bone metastases;
  - (e) The ultimate goal of treating patients with cancer and bone metastases is to reduce SREs, a composite endpoint including pain, bone fracture, spinal cord compression, hypercalcemia of malignancy and the need for surgery/radiotherapy for the management of symptomatic bone metastases.

**Correct answer:** c

**Comments:** SRE stands for skeletal-related events, and is a common composite endpoint of adverse bone outcomes for clinical trials testing drugs targeting bone metastases. Its avoidance may positively impact patients' quality of life, but it does not improve survival.

10. Regarding radiotherapy for the treatment of bone metastases, select the correct option:

- (a) It is used to prevent bone fractures, especially if mechanically unstable;
- (b) It cannot be used to treat diffuse bone metastasis;
- (c) It should not be used in combination with other treatments;
- (d) Complete pain relief happens most of the time more than 3 months after treatment
- (e) If pain relief is not achieved after first treatment course or symptoms reappear, re-irradiation might still be a treatment option.

**Correct answer:** e

**Comments:** re-irradiation is a treatment alternative if pain resurges. A minimum interval of 4 weeks between treatments is recommended and up to 2/3 of the patients will have pain relief after re-irradiation.

11. Are there multiple options of dose fractionation for conventional radiotherapy?

- (a) No, there is only one type of fractionation scheme, which is 8 Gy in a single fraction;
- (b) Yes, but 30 Gy in 10 fractions is the best fractionation that confers best pain control regardless of patient's fitness for the treatment;
- (c) Yes, there are multiple fractionation schemes and the best option will dependent on patient characteristics, tumor features, symptoms and previous treatments.

**Correct answer:** c

**Comments:** There are different hypofractionated schemes: 1) 30 Gy in 10 fractions/daily, 2) 20 Gy in 5 fractions/daily, and 3) 8 Gy in a single fraction. Different fractionation schemes are determined by patient characteristics, tumor features, symptoms and previous treatments.

12. In patients with uncomplicated bone metastasis, what is the best evidence-based fractionation scheme of conventional radiotherapy (CRT)?

- (a) 30Gy in 10 fractions is the best fractionation scheme that confers best pain control regardless of patient's fitness for the treatment;
- (b) 20Gy in 5 fractions is the best fractionation scheme that confers best pain control regardless of patient's fitness for the treatment;
- (c) A single fraction of 8Gy is non-inferior to other non-single fractionated schemes, feasible, easy to implement and cost-effective;
- (d) Single fraction CRT requires less re-treatment.

**Correct answer:** c

**Comments:** In the setting of uncomplicated bone metastases, i.e. presence of painful bone metastases unassociated with impeding or existing pathologic fracture, or presence of spinal cord or cauda equine compression, CRT with 8Gy/1fx is

non-inferior to other CRT fractionated schemes, feasible, easy to implement and cost-effective.

13. What is the indication for radiotherapy in the postoperative setting?

- (a) It should never be performed because patient already received an effective treatment;
- (b) It is indicated in patients with either axial or appendicular bone lesions with high quality evidence;
- (c) The most well established evidence supports its application in patients with spinal cord compression that received surgery as first treatment approach;
- (d) Given the generalized access and high quality evidence, SBRT should be proposed in the postoperative setting for all patients regardless of the estimated survival;
- (e) Metal implants are an absolute contraindication for postoperative RT, thus other materials should be used in the setting of surgical stabilization of bones.

**Correct answer:** c

**Comments:** despite the evidence supporting the use of post-operative CRT in the majority of bone metastases managed surgically, only the setting of spinal cord compression treated with surgery as first treatment approach was formally tested in clinical trials. The management of appendicular lesions with surgery plus CRT derives from retrospective analysis.

14. Regarding the use of surgery for the management of bone metastases, select the correct option:

- (a) Patient only benefit from surgery when there is a bone fracture or in case of spinal cord compression;
- (b) In patients with axial/spine metastases, the NOMS (Neurological, Oncologic, Mechanical and Systemic) decision framework is useful to decide if surgery is the best local treatment approach;
- (c) Risk of fracture is difficult to predict and besides physician experience there are no other tools to estimate this risk;
- (d) There are no other established invasive procedures to treat bone metastases besides surgery.

**Correct answer:** b

**Comments:** The NOMS (Neurological, Oncologic, Mechanical and Systemic) decision framework is recommended as a decision tool in the management of axial/spine metastasis. Other popular decision tool is the Mirels score for femoral lesions. Besides these scores, indication for surgical intervention should also take in consideration the expected functional impairment after treatments.

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# Chapter 50

## Brain Metastases



**Tiago Costa de Pádua, Adrialdo José Santos, Hakaru Tadokoro,  
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**Abstract** Metastasis to the brain is the most feared complication of systemic cancer, and it is the most common intracranial tumor in adults, being symptomatic in more than two-thirds of patients, with similar manifestations observed in primary brain tumors. Any patients with a cancer diagnosis who present with neurologic symptoms must be examined carefully and imaging studies must be performed to exclude BMs. With treatment, survival improves, but it is still discouraging. The management of BMs is divided in two major goals: symptomatic control and specific cancer treatment. It is essential to have a multidisciplinary team, and the patient should be a part of the decision-making process.

**Keywords** Brain metastasis · Supportive care · Radiotherapy

### 50.1 Introduction

Metastasis to the brain is the most feared complication of systemic cancer, and it is the most common intracranial tumor in adults, occurring in 20–40% of patients diagnosed with advanced cancer, which exceeds the frequency of primary tumors.

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The true incidence of brain metastases is unknown, but studies from the United States show an approximate incidence of 200,000 new cases annually. Recently, an increase in the incidence of brain metastasis (BM) was observed, which is probably due to an increased overall survival as a result of therapeutic advances and better radiologic examinations [1–4].

Any type of cancer can compromise the central nervous system (CNS), although in adults, lung cancer is the most associated with brain metastases (around 50% of all cases), mainly oat-cell carcinoma. Other neoplasms commonly associated with BM are breast cancer, renal cell carcinoma, colorectal cancer, germ cell tumor, and melanoma [3]. This was demonstrated in a large study by the Metropolitan Detroit Cancer Surveillance System, which estimated the incidence of BMs from 1973 to 2001. The study found a cumulative incidence of BMs of 9.6% for all primary sites combined, with the highest in the lungs (19.9%), followed by melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal (1.8%) cancers [4].

BMs can be single or multiple, and they are often found in the gray/white matter junction; 80% are found in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem. The mechanisms of metastases include hematogenous spreading or invasion by contiguity. Another possible mechanism is dissemination to the posterior fossa by the venous plexus of Batson, as in pelvic tumors [5, 6].

## 50.2 Clinical Manifestations

BMs are symptomatic in more than two-thirds of patients, with similar manifestations observed in primary brain tumors. Generally, the onset of symptoms is subacute, and BM has variable clinical features depending on the location, number of lesions, and associated complications (e.g., bleeding or hydrocephalus). In some cases, BMs can occur with intratumoral hemorrhage, and most are associated with melanoma and choriocarcinoma, which lead to an acute onset of symptoms.

The most common symptoms are due to an increase in the intracranial pressure (e.g., headache, nausea, and vomiting). Seizures, memory problems, mood or personality changes, and focal neurological dysfunction (e.g., ataxia, hemiparesis, and language disturbs) are other possible symptoms [7–10]. However, 10% of patients may be asymptomatic, and the BM is discovered after cranial imaging as part of disease staging.

BMs can occur as the first manifestation of cancer (observed in 5–10% of all patients), and they can present synchronously with systemic and intracranial cancer (5–10%). However, it is more common for them to present metachronously after the diagnosis of systemic cancer (>80% of all patients).

## 50.3 Diagnosis

Any patients with a cancer diagnosis who present with neurologic symptoms must be examined carefully, and imaging studies must be performed to exclude BMs. Usually the first examination is CT of the brain, because it is an easily accessibility

and inexpensive diagnostic tool that shows lesions with circumscribed margins, associated vasogenic edema, and localization at the junction of the grey/white matter. However, there is a great deal of variability in the appearance of these tumors.

MRI with contrast enhancement is the preferred exam, because it has a better sensitivity and specificity than other imaging modalities for determining the presence, location, and number of metastases. The aspect is typically iso- to hypointense on T1- and hyperintense on T2-weighted images. **Spectroscopy shows** intratumoral choline peaks with no choline elevation in the peritumoral edema [11, 12].

Differential diagnosis includes primary brain neoplasm (especially glioblastoma), cerebral abscess, subacute stroke, and demyelinating diseases [9].

In patients with unknown primary cancer and BMs, a history and physical examination are the first steps, followed by imaging studies. The lung should be the primary focus of evaluation because of the high prevalence of BMs in this type of tumor. The use of blood markers (i.e., the carcinoembryonic antigen [CEA], alpha-fetoprotein, prostate-specific antigen [PSA], and Ca-125) and endoscopic exams should be realized upon suspicion. PET-CT may be used as part of the investigation, and biopsy should be reserved for cases with doubt or when the primary site is not identified [13, 14].

## 50.4 Prognostic Factors

The most used prognostic classification system was created by the Radiation Treatment Oncology Group, which uses recursive partitioning analysis (RPA). There are three prognostic classes with important differences in survival [15]. Class 1 patients (16–20% of all patients) have the following: a Karnofsky Performance Status (KPS) >60, aged <65 years, and no evidence of extraneural metastases or controlled primary cancer. Class 3 patients (10–15% of all patients) have a KPS <70 and class 2 patients (65% of patients) include all patients that cannot be classified under class 1 or 3.

Other known prognostics factors include the following: the performance status, age (<65 years), a favorable tumor histology, controlled primary disease, isolated brain disease, and solitary versus multiple tumors [9, 10, 16].

## 50.5 Treatment

In general, patients with BMs typically have a mean survival of 1 month without treatment. With treatment, survival improves, but it is still discouraging. The management of BMs is divided in two major goals: symptomatic control and specific cancer treatment [16].

### **50.5.1 Symptomatic Treatment**

Symptomatic treatment includes the management of brain edema, hydrocephalus, prophylaxis of seizures, and possible complications. The first step consists of administering steroids and anticonvulsants. Steroids are used to minimize vasogenic edema, which leads to an improved clinical condition. The most used steroid is dexamethasone, an empiric dose of 4–16 mg daily, because it is the most potent, has the best CNS penetration, and the least mineralocorticoid side effects. As the clinical situation permits, the lowest dose of dexamethasone that controls the symptoms should be used in order to avoid adverse effects [7, 8, 16, 17]. Symptomatic treatment with steroids alone prolongs survival for approximately 2.5 months.

Seizures are one of the most common symptoms in patients with BMs that occur in >25% of all cases and the use of antiepileptic drugs (AEDs) is recommended after the first episode and for prophylaxis immediately following surgical resection. There are no rules regarding the use of AEDs as prophylaxis for seizures in patients without a previous history of seizures [18]. Among the classes of AEDs, non-enzyme-inducing AEDs such as pregabalin, lamotrigine or topiramate are preferred to avoid drug interactions with others drugs and chemotherapy [19].

BMs are associated with an increased risk for venous thrombosis due to a hypercoagulable state, with an estimated incidence of 20% in this patient population. The main treatment is anticoagulation with a low molecular weight (LMW) heparin or warfarin. LMW is preferred because of its increased effectiveness in preventing recurrent thromboembolism, it has no interaction with other drugs, and it is convenient. In case of metastases associated with an increased risk of hemorrhage (e.g., melanoma, choriocarcinoma, thyroid carcinoma, and renal cell carcinoma) the use of an inferior vena cava filter is recommended [10, 20]. Prophylaxis with anticoagulant is not routinely indicated, and it should be reserved for the perioperative period [21].

### **50.5.2 Specific Treatment**

Specific treatment can be realized in three main modalities, usually in combination with radiation, systemic therapy with chemotherapy, and surgical resection. The goals are to prolong survival and improve quality of life, and the approach is based on the characteristics of the tumor (i.e., the size, location, and number of metastases), KPS, patients' age, and prognosis [7–10, 16]. According to the features and RPA classification, patients with a good prognosis must be treated aggressively in an attempt to eradicate or control the disease in the brain. In patients who are not candidates for this approach, best supportive care or only whole brain external beam radiation is indicated.

Radiotherapy remains the most used treatment and includes whole brain radiotherapy (WBRT) and stereotactic radiosurgery. WBRT is preferred in cases with

multiple metastases or solitary metastases associated with extensive systemic disease in order to control the symptoms and improve quality of life [22]. WBRT can also be used after resection of brain metastases, reducing the risk of intracranial relapse and improving survival, as shown in randomized trials [23–25]. The most used protocol consists of whole brain irradiation (a total dose of 30 Gy among 10 sessions) with concomitant use of dexamethasone to reduce acute complications [16].

Stereotactic radiosurgery is a new modality of radiotherapy that provides an intense focal irradiation on a small lesion using multiple well-collimated beams that reduced radiation damage to adjacent tissue. This is important in cases with lesions in eloquent or inaccessible areas that have similar outcomes compared to surgery. Other advantages are less toxicity than WBRT, and there is no need to discontinue systemic therapy. BMs from non-small cell lung cancer, renal cell carcinoma, and melanoma that are radio-resistant show good response rates with this treatment [16, 26–29].

Surgery is another option, especially for large symptomatic solitary BMs, cases with a doubtful diagnosis or unknown primary site, and symptomatic control in cases with a significant mass effect from the tumor. Some characteristics should be evaluated before the indication, which include the accessibility and resectability of the tumor. Recent advances in neuro-oncological surgery have led to a reduced risk of morbidity and mortality with this kind of procedure.

Historically, chemotherapy has had a limited role in the treatment of BMs because of the low penetration in the CNS, and few clinical trials support the use of chemotherapy for BM treatment. Generally, it is reserved for patients with a poor response to other modalities or with chemosensitive tumors (e.g., lymphomas, germ cell tumors, and small cell lung cancer) [30, 31]. More recently, trials with immunotherapy and targeted therapy have shown efficacy in some tumors (e.g., using lapatinib for breast cancer, gefitinib for non-small cell lung cancer, and ipilimumab for melanoma) [32].

In conclusion, BMs are becoming more frequent, and treatment is a challenge for oncologists. It is essential to have a multidisciplinary team, and the patient should be a part of the decision-making process. Patients should also be included in palliative care programs as soon as possible.

### ***50.5.3 Prophylactic Cranial Irradiation***

Prophylactic cranial irradiation (PCI) is indicated in patients who are diagnosed with limited stage non-small cell lung cancer who have achieved complete remission after primary treatment in attempt to reduce intracranial relapse and improve survival. This should be considered in cases with extensive disease, a good performance, and a good response. However, the impact on overall survival is not clear. Thus, it is necessary to consider the possible toxicity associated with PCI, especially in young patients [33–36].

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# Chapter 51

## Chapter – Palliative Care



Caroline Souza dos Anjos and Débora Souza Gaudencio Feijó

**Abstract** The term hospice was coined in medieval times to denote rest homes for pilgrims, travelers and foreigners who needed shelter for temporary rest. Hospices then reappeared in the history of mankind in mid-nineteenth century as places where severely ill persons received end of life care. Usually managed by religious orders, they also sheltered the indigents and patients with “incurable” diseases.

**Keywords** Palliative care · Pain · End of life

### 51.1 Palliative Care History and Concepts

The term hospice was coined in medieval times to denote rest homes for pilgrims, travelers and foreigners who needed shelter for temporary rest. Hospices then reappeared in the history of mankind in mid-nineteenth century as places where severely ill persons received end of life care. Usually managed by religious orders, they also sheltered the indigents and patients with “incurable” diseases [1–3].

The year 1967 marks the beginning of the modern Palliative Care movement when the St. Christopher hospice was inaugurated by the palliative physician Cicely Saunders. However, within this context, the Palliative Care term was first cited in Canada by the surgeon Balfour Mount in 1975 [4–8].

The conceptual history of palliative care varies according to historical and cultural reasons, although it is intrinsically related to chronicity and to the dying pro-

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cess. The study of the intersection between magic and ritualistic thinking, which serves as a tool for coping with pain and death, may probably lead to the understanding of the origin and evolution of what has been known as palliative care along time [3]. Thus, the meaning of palliative care may be temporally related to the different postures adopted by man when faced with the diagnosis of a serious disease with no possible cure and with the sensation that death is close [9].

The palliative term, in turn, comes from the Latin *palliare* and generically designates the action of covering and dissimulating. The noun *pallium* means a cape, a mantel or any type of clothing used as protection in order to cover the body, the face or the identity of a person. Within the context of care, a palliative action can be interpreted as a therapeutic action to be used to attenuate the problems secondary to a disease, although without the objective of definitely solving the problem or providing a cure [10, 11].

With her practice of humanized and individualized medicine focused on the human being and not on the patient, Cicely Saunders started a form of multidimensional approach to the control of the symptoms inherent to falling ill in order to guarantee the maximum possible quality of life to the patients and their relatives when facing a progressive functional worsening. By recognizing the importance of the appropriate treatment of pain and of symptom management, she designated the concept of “total pain” and described the importance of dealing with the emotional, psychosocial and spiritual aspects of the patient and his relatives [12, 13].

Focusing on the human being, Cicely Saunders stated [14]:

*...A little boy separated from his mother may be completely safe, but does not feel safe. A little boy in the arms of his mother during a bombing raid may be very little safe, but he feels completely safe. We need to make all our patients feel safe...*

In the 1990 decade, the World Health Organization (WHO) defined Palliative Care as a modality of care and a strategy of intervention in public health. Since then, many countries have validated this approach, thus promoting a considerable increase in the discussion of this theme in education and in research, with one of its focal points being the training of professionals habilitated in palliative care [5, 6].

According to Gomez-Batiste (2017), Palliative Care is based on the following concepts [6]:

*Palliative Care is the prevention and relief of suffering and the promotion of dignity, of a better quality of life and of adaptation to diseases of progressive evolution, destined to adults and children who live with serious, chronic and complex problems that threaten the continuity of life and their relatives. Due to the regional, cultural and temporal changes regarding the the most common and severe types of suffering, the conceptual definitions and the populations included in care may change, as is also the case for palliative care itself*

If we consider the physical, psychological, spiritual and social aspects of all patients and their caregivers, Palliative Care will emerge as an essential necessity in view of the increased incidence of chronic diseases and the absence of therapies that can modify the course of illness [15]. The importance of integrated medical care should be emphasized, i.e., in addition to specialized medical care for chronic clinical conditions, Palliative Care should be provided in a flexible and concomitant

manner, and not just when the disease involves frank clinical deterioration. The reason for this is due to the multidimensional necessities already mentioned above since the patient and his relatives suffer with the progressive course of an illness in an advanced stage, with repeated hospital admissions and diverse demands as time goes by [4–6].

## **51.2 Principles of Palliative Care**

Palliative care can be defined as an approach to improve the quality of life of patients and their families facing life-threatening illness, through the prevention, assessment and treatment of physical, psychosocial and spiritual problems. The principles of palliative care are summarized below.

### ***51.2.1 To Provide Relief from Pain and Other Distressing Symptoms***

Patients diagnosed with an advanced stage and/or life-threatening illness in general experience multiple symptoms, such as pain, depression, anxiety, confusion, fatigue, breathlessness, insomnia, nausea, constipation, diarrhea, and anorexia [16]. These symptoms result from a variety of factors. For instance, advanced cancer patients with bone and pleural metastases may have symptoms (eg, bone pain and dyspnea) resulted from the disease, from treatment itself (eg, bone and muscle pain after use of osteolysis inhibitor), or from other concurrent conditions (eg, back pain due to a herniated disk).

Exploring patients' reports of symptoms and their dimensions (severity, frequency, level of interference with activities, and level of distress associated with the symptom) is a fundamental aspect of patient-centered care, requires patience and persistence. The current literature suggest cancer patients undergoing treatment may have better health-related quality of life and better survival if they self-report symptoms to the oncology team [17, 18]. Health care providers tend to underestimate symptom severity, what can lead to missed opportunities for diagnosis and symptom relief [19].

Each identified symptom should be further investigated in regard to its Onset, Palliating and Provoking factors, Quality, Response to previous treatments, Related factors/symptoms, Severity and Temporal characteristics, as well as the Meaning of the symptom/burden to the patient [20]. Comprehensive symptom assessment can contribute to significant symptom improvement and better quality of life [21, 22]. Periodic symptom reassessment is necessary for monitoring the response to specific symptomatic interventions and possibly modifying treatment goals.

Over the last 30 years the use of rating instruments completed by patients themselves represents a major change in symptom assessment. The approach to rating pain relies on patient's reports by rating severity, using a verbal or numerical scale of 0–10, where 10 is worst. Nevertheless, for many symptoms there is no clear evidence about the optimal cut points are to define symptom severity [23].

A number of challenges for symptom assessment may be encountered by the palliative care team: some patients are unable to rate their symptom severity on a numerical scale; seriously symptomatic patients, for example with severe fatigue, may only be able to answer some questions briefly; patients who are confused or delirious will not cooperate properly [24]; patients may downplay or not report symptoms (particularly pain) because of fears that worsening symptoms reflect disease progression and that the oncologist will stop treatment; language and cultural factors can pose barriers [25].

### ***51.2.2 To Affirm Life and Regards Dying as a Normal Process***

Death is a normal process and an important stage of humans lives, but unlike birth, people avoid talking about it. Although it is a hard work for everyone (patient, family, friends and care providers), those accompanying the journey of the dying and their families report death as an experience that can be transformative, a time of spiritual growth, and a legacy for the loved [26].

Palliative Care brings the possibility of death as a natural and expected event in the presence of life threatening disease, emphasizing the life that can still be lived.

### ***51.2.3 To Intend Neither to Hasten or Postpone Death***

Differently from euthanasia that proposes to accelerate death motivated by empathy to patient's suffering or distanasia prolonging life at any cost, orthothanasia is the natural death, without neither disproportionate nor lacking treatments [27].

### ***51.2.4 To Integrate the Psychological and Spiritual Aspects of Patient Care***

The life-threatening illness, usually brings a series of losses (autonomy, self-image, security, physical ability, respect, employment, purchasing power) and consequently psychological issues such as anguish, depression and hopelessness [28]. The approach of these aspects from psychological perspective is fundamental.

Coping refers to adjustments and psychological rebalancing after a life-threatening illness diagnosis. Adaptive process may utilize a number of factors and styles, including humor, planning, active management, disclosure and sharing with others/seeking support [29]. Advanced cancer patients with dependent children require particular attention, once they are at high risk for psychiatric distress and poor quality of life (QOL) [30].

Clinicians should be sensitive to comments that might indicate spiritual distress. Patients may express spiritual need with comments that hint at an underlying fear, despair, guilt, desire for a hastened death, or hopelessness. Spiritual assessment is recommended in guidelines from the Consensus Conference on Quality of Spiritual Care as a Dimension of Palliative Care [31]. There are some formal tools available for obtaining a spiritual history [31, 32]. The spiritual assessment, is best completed by a trained chaplain/counselor using open dialogue and empathic listening.

### ***51.2.5 To Offer a Support System to Help Patients Live as Actively as Possible Until Death***

To live actively, not simply live, refers to the question of survival “at any cost”. A good death may be the one free from avoidable suffering for patient, family and caregivers, in general respecting patient’s and family’s wishes, and reasonably consistent with clinical, cultural, and ethical standards [33].

### ***51.2.6 To Offer a Support System to Help the Family Cope During the Patients Illness and in Their Own Bereavement***

The family, both biological and acquired (friends, partners, etc.), can and should be valuable collaborators to end-of-life care delivery. In the same way, they also suffer and their suffering must be addressed.

It is importante to assess psychological distress and coping among family and caregivers, as well a preventing and treatment plan must me made in order to reduce risk of posttraumatic stress and prolonged grief disorders [34]. Screening for psychological morbidities among caregivers can utilize the same items and approaches that are used for patient assessment.

### ***51.2.7 To Use a Team Approach to Address the Needs of Patients and Their Families, Including Bereavement Counselling, If Indicated***

A number of factors will simultaneously contribute to the modification of the therapeutic response, the evolution of the disease itself and the relationship with the patient and the family. Palliative Care team should look at all patient's dimensions to develop an approach plan, the multiprofessional team with multiple "looks" and individual perception can carry out this work in a comprehensive way.

Patients with advanced illness and their caregivers frequently experience profound financial and social strain [35]. Family and friends provide most of the assistance to terminally ill patients, for a mean of 43 h per week [36]. Almost one-third of the families of seriously ill adults report loss of all or most of their savings due to the illness and need for caregiving [37]. Furthermore, economic burden may profoundly impact healthcare decisions [38].

### ***51.2.8 To Enhance Quality of Life, and May Also Positively Influence the Course of Illness***

Quality of life and well-being implies an observation of several dimensions of life. It is very important to understand the patient's priorities and goals for symptom relief as well as values and preferences, their prognostic awareness, understanding of the illness and treatment should be systematically assessed. Social resources, access to services, medicines and other resources should be included among the aspects to be addressed by the multiprofessional team [39, 40].

With a holistic approach observing the patient as a biographical human being rather than simply a biological being, respecting needs and wishes, it is possible to improve the illness course and even to increase survival. Living the remaining time with quality.

## **51.3 To Whom Palliative Care Is Indicated?**

Services may be delivered under the specifications of hospice, if the patient has a prognosis of 6 months or less and is willing to focus care on palliative and comfort-oriented services as opposed to life prolonging treatments. Palliative care services can be provided in the hospital, ambulatory setting, nursing home, or at home [41, 42].

A systematic review highlighted the lack of consensus in the literature on which patients should be referred in the ambulatory setting, and described cancer prognosis, physical symptoms, performance status, psychosocial distress, and end-of-

life care planning needs as factors that should be considered for appropriate referrals [43]. Furthermore, raising awareness of ways in which subspecialty palliative care complements standard oncology care and developing ways for oncologists and palliative care physicians to collaborate and integrate their respective skills may help [44].

The World Health Organization (WHO) determines that palliative care must be initiated for all patients with serious, progressive and incurable diseases that threaten the continuity of life since the diagnosis. For a recent metastatic cancer diagnosed patient, palliative care should be provided early in the course of illness, at the same time as curative or life-prolonging therapies, such as chemotherapy or radiation therapy [45].

## 51.4 Multiprofessional Team

Palliative care team should be formed by physicians as well as nonphysician members, such as nurses, counsellor or psychologist, occupational therapist or physiotherapist, pharmacist, dietitian and social worker.

A multidisciplinary team is a group of healthcare professionals of varied competencies and roles, working together towards a common goal of providing optimal care for a patient [46]. Palliative care lends itself particularly well to this approach because of the multiple dimensions involved in caring for palliative patients as mentioned before in previous section.

## 51.5 Communication in Palliative Care

In view of the demands described, a fundamental pillar of Palliative Care is communication in all its dimensions and in all its aspects [47, 48]. A good palliative care professional is used to practicing welcoming listening without prejudice and, in addition to validating all the anguish of relatives and caregivers, he exercises all the essential aspects of nonverbal communication in his daily practice [48].

The relatives of critically ill patients appreciate communication of quality with the health team responsible for the care. When performed in an effective manner, communication generates family satisfaction, well-being and mental health. Since the establishment of a therapeutic alliance between the health team, the patient and relatives/caregivers is extremely necessary, it is imperative to promote an effective exchange of information, to generate integration between the health team and the caregivers and to habilitate the latter to participate in an active manner in therapeutic decision making [49, 50].

Patient reports described in qualitative studies emphasize the importance of concepts such as goodness, compassion and dignity, in addition to the importance of the



emphasis on time devoted to “caring for the patient” and not “to doing to the patient”, always giving priority to empathetic and welcoming listening [48].

Communication between patient and health professional is not always considered to be therapeutic. Countless situations of clinical practice demonstrate that words, expressions and attitudes may wound the patient and generate hostility and barriers in the process of communication, thus disrupting the tie with the health team. On this basis, communication may become iatrogenic. The imprudence of a professional related to the inappropriate perception or poor utilization of nonverbal communication in the interaction with the patient may be considered to be iatrogenic since it can generate painful psychological sequelae and compromise the care process [51–55].

The nonverbal language is a reflex of a personal emotional status and therefore it is subjective, as also are one’s feelings [56]. Since these feelings are considered to be socially negative, the patient does not verbalize his sadness, anger, shame, fear, but he can express these feelings in a nonverbal manner, usually in an unconscious manner though the tone of his voice, facial expression, gestures and body posture. Since the expression of signals is an often unconscious action, it cannot be dissimulated by an individual [57, 58].

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