PROTON THERAPY IN ONCOLOGY

A GENERAL OVERVIEW OF CURRENT PRACTICE, OPPORTUNITIES AND CHALLENGES

Proton Therapy in Practice: Clinical Indications – General Introduction

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FOREWORD

Since IBA first started to develop proton therapy solutions, we have focused on collaboration and the sharing of information. This culture of cooperation allows us to work collectively with clinical partners to make proton therapy available to anyone who needs it.

Our purpose is simply to offer more cancer patients a better quality of life.

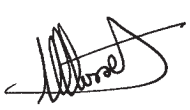
The amount of clinical data on proton therapy is increasing rapidly, making it a challenge to keep up with new findings and advancements. We decided to take advantage of our day-to-day involvement with experienced clinical teams from proton therapy centers worldwide, and gather and share information on the use of proton therapy in oncology.

We've compiled this information in a series of white papers on the latest scientific and clinical advances in proton therapy. The information that follows is the result of our in-depth review of the latest articles published in key scientific journals.

We have undertaken this information-gathering exercise with honesty and ethics. While all care has been taken to ensure that the information contained in this publication is correct, unbiased and complete, the reader must be aware that articles have been selected and data interpreted. We invite you to treat this data with care, exercising your own critical and scientific judgment.

The IBA team believes in the benefits of proton therapy for patients and society. We hope that this information will help you and your team learn more about the extraordinary promises of proton therapy, so that we can continue to make it accessible to more patients.

We wish you a good reading,



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Average life expectancy worldwide has increased by about six years over the last two decades, according to the "World Health Statistics 2014". However, cancer remains one of the leading causes of morbidity and mortality, accounting for 8.2 million deaths in 2012. Its incidence grows yearly at an average rate of 2.3% and it is expected that annual cancer cases will rise by about 70% within the next two decades, from 14 million in 2012 to 22 million. About 30% of this rise is due to the main five behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol. Other major influences include ageing population and pollution. The most common causes of cancer death are lung cancers (1.59 million), liver (745,000), stomach (723,000), colorectal (694,000), breast (521,000) and esophagus (400,000).[1]

INTRODUCTION

Combatting cancer and treating this growing number of patients using the latest medical advances has gained prominence among medical professionals and healthcare policy makers. Radiation therapy takes up a major part of investments to fight cancer since 523 (52%) out of every 1,000 new cancer patients will need radiation therapy as part of their treatment. Out of these, 120 patients (23%) will require re-treatment.[2]

Proximity and timely access to radiation therapy facilities are known to affect treatment outcomes. Nevertheless, many countries lack sufficient radiation therapy facilities with regard to their number of patients. In some, radiation therapy options are non-existent. With reference to the

World Health Organization's requirement of 2 to 3 Linacs (linear accelerators) per million population, there is still work to be done to assure better global access to this effective and critical cancer treatment component.

A wide range of advanced radiation therapy techniques and technologies are available, such as brachytherapy, Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), Stereotactic Body Radiation Therapy (SBRT) and others. Some are administered by introducing a radioactive source, e.g. Iridium-192 or Iodine-135, into the body inside or near the tumor, while external beam therapies are delivered through Linacs. Depending on the external radiation source type and delivery technique, the dose conformity and low/medium dose bath may vary, resulting in different outcomes for the patient.

Photons are the most common type of ionizing radiation, but heavier particles such as electrons, neutrons, carbon ions, alpha particles and protons may be used to administer radiation therapy as well. Due to the physical properties of protons, which stop at a given depth and deliver the largest part of their energy at the end of the "Bragg Peak", the beams deliver equal or higher radiation to the target while conveying less dose to surrounding healthy tissues.

Leading doctors and medical physicists have embarked on expanding the clinical application of proton radiation therapy. By now, the value of this treatment modality for pediatric cancers is widely recognized. It therefore attracts special attention from the medical community, leading to numerous discussions about the need for a proton facility to provide more advanced treatment options and how these could equally benefit adult cancer patients.

This white paper details the science and clinical utilization of proton radiation therapy. It aims to provide information that facilitates discussion and evaluation of a proton therapy facility's value.

1. HISTORY OF PROTON THERAPY

Proton beams are ionizing radiation, which makes proton therapy part of the broad family of radiation therapy and an indisputable technique for treating cancer. Ionizing radiation destroys cancer cells by causing their DNA to malfunction (it breaks their DNA strand). There are two

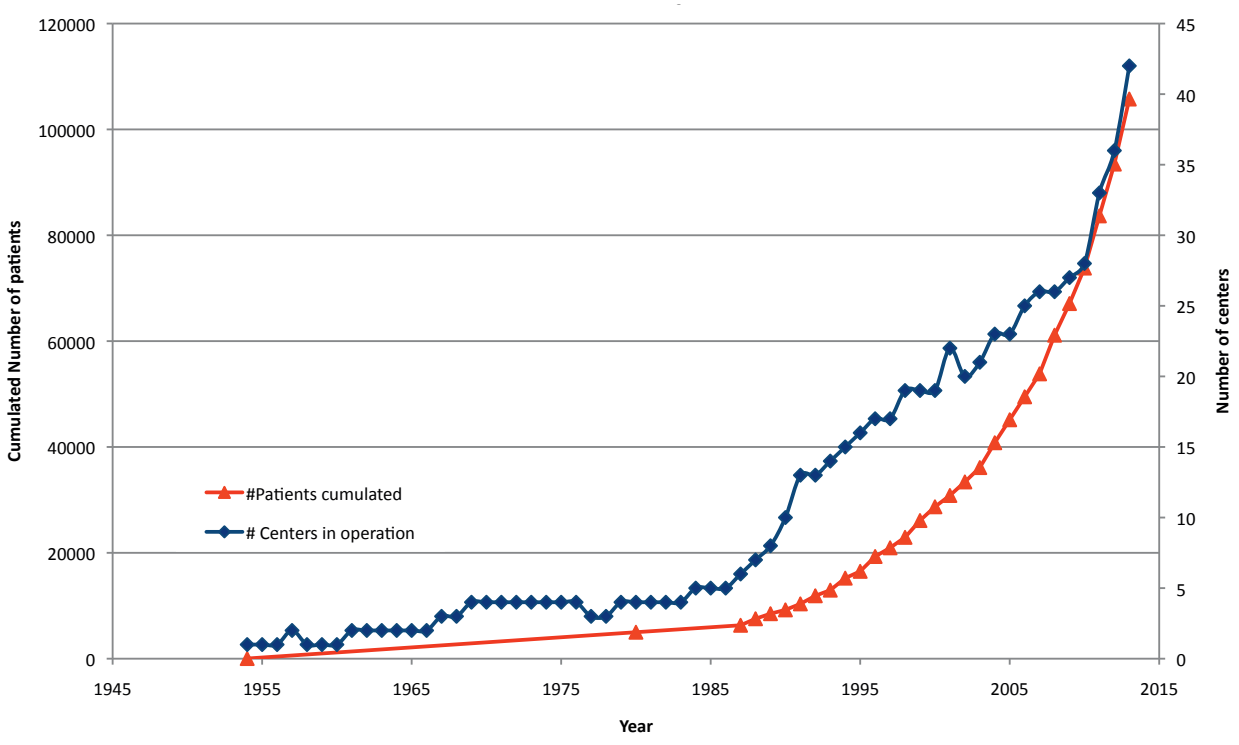

Figure 1.1: Graph representing the evolution of proton therapy centers under clinical operation and the cumulated number of patients treated using proton therapy (Source: PTCOG Website)

kinds of radiation therapy: external, and brachytherapy. External radiation therapy uses an ionizing radiation source originating outside the patient's body, while brachytherapy works by inserting a radioactive source in the body, either in a cavity, by needles slid into the impaired organ, or through a permanently implanted source. Proton therapy belongs to the external radiation therapy category, among other types of ionizing radiation such as photons, electrons, carbons, neutrons, etc. (non-exhaustive list).

In 1946, Robert Wilson was the first to suggest using accelerated protons and heavier ions for radiation treatment. The first patient was treated eight years later, in 1954, at University of California, Berkeley. Three years later, The Gustav Werner Institute in Uppsala, Sweden, accomplished the same achievement for the first time in Europe.[2, 3]

Proton therapy was originally confined to a very few centers around the world and typically practiced in a research environment. However, since those early days, more than 130,000 patients have been treated by protons and the number of active centers worldwide has risen to 58.[4] The first hospital based proton therapy system was installed in 1990 at the Loma Linda University Medical Center in California.[2] Today, 58 proton therapy centers are in operation worldwide[4] and several additional centers are currently in different stages of deployment.[5]

More than 25,000 patients had already been treated with proton therapy in the late 90's when the IBA Proton Therapy System was introduced at Massachusetts General Hospital,[4] while millions of others had undergone radiation therapy with photons. Each year, more than 12,000 cancer patients receive proton therapy worldwide. Out of the 130,000 cancer patients who received proton therapy so far, more than 30,000 have been treated using a proton therapy system developed and installed by IBA. The data and studies presented in this and subsequent papers represent the results obtained from proton therapy treatment, irrespective of the equipment provider.

2. GENERAL RELEVANCE OF PROTON THERAPY: FROM BALISTIC TO CLINICAL ADVANTAGE

As the energy deposition of protons differs from the one of photons (through the Bragg Peak), this treatment modality enables radiation oncologists to better shape the dose on and around localized targets, avoiding their surroundings and therefore reducing the integral dose and the potential side effects in healthy surrounding tissues.[6]

Figure 2.1 represents the comparison of the relative dose deposition in depth for high energy photons, single Bragg Peak Protons and Spread Out Bragg Peak Protons (SOBP). The illustration shows that, compared to the standard

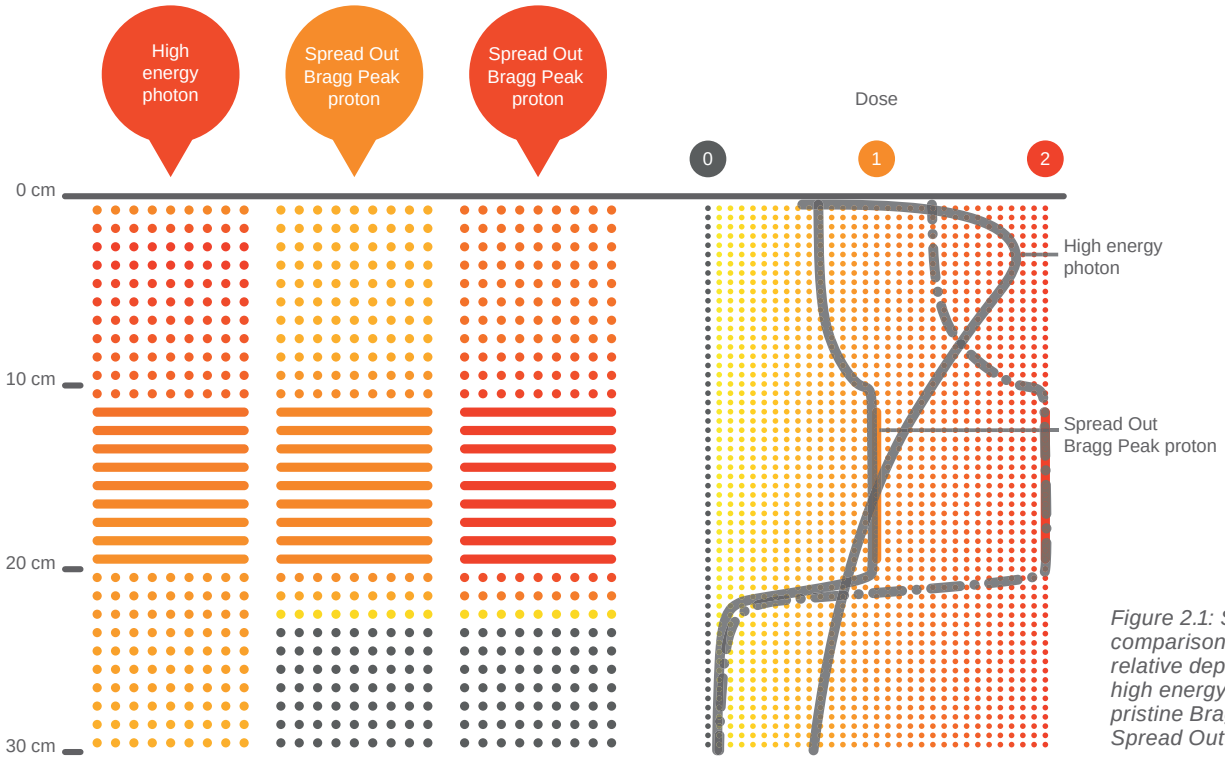

Figure 2.1: Schematic comparison of depth dose relative deposition for high energy photons; pristine Bragg Peak; Spread Out Bragg Peak

dose delivery using photons, the proton field delivers the requested dose at the target while deposing no dose beyond the SOBP and a lower dose in front of it to obtain the same dose level at a given depth through a single field.

In clinical practice, the dose is delivered to the target using various techniques. For photons, these include 3D Conformal Radiation Therapy (3DCRT), Intensity Modulated Radiation Therapy (IMRT), Stereotactic Body Radiation therapy (SBRT) and Volumetric Modulated Arc Therapy (VMAT) or Helical Tomotherapy (HT). The following two techniques lend themselves to delivering protons: Broad Beam Technique or Intensity Modulated Proton Therapy (IMPT).

Various techniques are in use because the purpose (in both photons and protons) is to focus the dose on the target while minimizing dose delivery to the surrounding tissues. Depending on the technique used, dose distribution will vary.

The superior beam properties of protons over photons can be translated into clinical benefits using different strategies (figure 2.1):[7, 8, 9]

- a dose escalation inside the tumor while keeping the side effects to a level similar to IMRT
- lowering the dose to normal tissues while keeping the target dose the same
- reducing the low dose bath and the risk of secondary malignancies following treatment
- embracing it as the treatment of choice for retreatment

On top of the physical advantages, proton beams do have a Relative Biological Effectiveness (RBE) – the ratio of photon dose required to cause an equivalent biological level of effect as a given proton dose – at 1.1.[10]

3. CLINICAL INDICATIONS AND PATIENT SELECTION

The physical and biological properties of proton beams lead to the advantageous quality of dose distribution, resulting in improved therapeutic gains as discussed in chapter 2. The clinical interest lies in the comparative impact of proton beam therapy, either with a curative intent or as a salvage treatment for cancerous and noncancerous conditions versus alternatives such as photon beam therapy. This distinction can effect survival, disease progression, safety, health-related quality of life and other patient outcomes.

An increasing emphasis on evidence-based medicine makes it worthwhile to assess the evidence available to support the choice of proton therapy over other current techniques so as to better guide the physician and patient toward the most appropriate treatment.[11]

The present policy developed by the American Society for Radiation Oncology (ASTRO) recommends basing patient selection on the added clinical benefit proton therapy offers. This comes down to considering proton therapy in such cases where sparing the surrounding normal tissue is crucial and cannot be adequately achieved with photon-based therapy. The policy provides several non-specific examples:

- The target volume is in close proximity to one or more critical structures, and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to those structures.
- A decrease in the amount of dose inhomogeneity in a large treatment volume is required to avoid an excessive dose “hotspot” within the treated volume to lessen the risk of excessively early or late normal tissue toxicity.
- A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity.
- The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Fully leveraging proton therapy’s dosimetric advantages adds complexity to the treatment compared to other kinds of radiation therapy. A thorough comprehension by oncology professionals of the benefits and consequences is therefore indispensable.[12]

4. WORLDWIDE CLINICAL TRIALS STATUS AND OUTLOOK

Evidence-based medicine requires the demonstration of high levels of clinical evidence. In 2008, Terasawa et al. reviewed the clinical studies of particle-beam therapies: 76% out of 243 studies were retrospective cohort studies, and they counted 35 prospective single-group trials, 13 non-randomized comparative studies (NRS) and 8 randomized controlled trials (RCT).[13] In 2009, Tufts Medical Center, Boston, investigated the clinical studies for the Agency for Healthcare Research and Quality of the

US Department of Health. It identified 10 RCTs and 13 NRS's. The RCTs were mostly conducted in the USA and focused on ocular, head and neck, and prostate cancers.[14]

Six years later, in August 2015, 122 prospective clinical trials were registered on ClinicalTrials.gov with a current status of 'recruiting'. RCTs have increased to 20 and NRS's to 29. Clinical trials using proton radiation therapy are now being conducted with increasing frequency. In 2009 there were no RCTs conducted for brain, skull base, glioblastoma, chordoma and pediatric cases and 2 for head and neck. There were equally no NRS's for pediatric, brain, skull base, glioblastoma and chordoma and only 1 for head and neck. In 2015 numbers have risen to 2 RCTs and 6 NRS's for head and neck and 5 RCTs and 6 NRS's for brain, skull base, glioblastoma and chordoma.

Due to the larger number of installed base and patient load, 90% of clinical trials are led by USA- based institutes. Renowned radiation oncology centers that have proton facilities continue to lead the research effort (table 4.1).

	Y2009	Y2015
Randomized studies	10	20
Non-randomized comparison studies	13	29
Total number of prospective studies	58	122

Table 4.1: Number of ongoing RCT and Non-Randomized Comparative Trials in 2009 and 2015

5. FUTURE DEVELOPMENTS IN PROTON THERAPY AND NEW EVIDENCE

Proton Beam Therapy has existed for over 50 years, not only making significant progress from research centers to clinical application, but evolving at high speed toward increasing refinement. Improvements in both the technology and its application help to unlock its full clinical potential step by step:

5.1 PENCIL BEAM SCANNING

Pencil Beam Scanning (PBS) is the next-generation delivery technique. It opens the door to Intensity Modulated Proton Therapy (IMPT) which achieves much higher levels of conformality to the target while further decreasing the level of dose to the surrounding tissues in comparison to the broad beam technique.[15, 16, 17] The considerable advantages of IMPT lead to the expectation that the majority of existing proton therapy centers will convert to this new modality within the next few years.

5.2 SINGLE-ROOM SYSTEMS

Single-room PBS systems have been introduced. These offer the latest technologies used in multiple-room centers in a more compact setting. The outcome data presented in this white paper mostly refers to studies conducted using the broad beam delivery modality also called double scattering. Better results than those available today will gradually be substantiated as PBS and its inherent advantages over broad beam find their way into the treatment room and become widely used.

5.3 ADAPTIVE TREATMENT

Present-day proton therapy systems are equipped with volumetric imaging modalities: either a Cone Beam CT, installed at or very near the treatment isocenter, or an in-room CT-on-rails. The first purpose of both imaging tools is to improve the accuracy of patient positioning, but they also open up possibilities for anatomical modification assessment, paving the way to adaptive proton therapy treatment. Additionally, these imaging modalities may further widen the gap between proton and conventional radiation therapy when it comes to reducing treatment toxicity.

5.4 MOTION MANAGEMENT

As PBS is a dynamic delivery technique, intrafraction motion of the organs and the target inside the patient will have an impact on dose uniformity: the so-called interplay effects.[18]

Proton therapy systems using PBS are currently equipped with countermeasures designed to reduce these effects. Rescanning and gating can be listed among these functionalities. They allow the clinical team to set different parameters, such as the number of rescannings or the duty cycle, in order to accord the target amplitude and frequency in such a way that the dose variation is reduced below a value that would clinically impact the quality of treatment.[19]

With such countermeasures in place, PBS lays the groundwork to confront the more challenging tumors with proton therapy as well.

5.5 NEW EVIDENCE

There is no doubt that novel medical technologies must offer high-level clinical evidence through robust comparative controlled research. However, several authors

remarked that the 'rules of evidence' of the randomized approach aim at the evaluation of efficacy, which appears to be not as well-suited in proton radiation therapy where evidence is mainly related to adverse effect reduction and normal tissue protection.[8, 20, 21] When the UK government approved two new proton facilities for the country, the assessment was not done by the National Institute for Health and Clinical Excellence, commonly known as NICE. The UK report states that 'there is extensive evidence of the superiority of dose distribution. The scarcity of the resource and the timescales for the expression of late side effects has meant it has not been possible to construct conventional clinical trials and provide the sort of evidence that would lend itself to NICE methodology.'[14] A suggested additional methodology is to combine the NTCP (Normal Tissue Complication Probability) model and comparative planning studies in order to predict the outcome and better select the population for which the use of proton therapy as a treatment modality will be of the greatest benefit. This approach represents a first step toward personalized medicine.

6. COST EFFECTIVENESS AND HEALTH ECONOMICS OF PROTON RADIATION THERAPY

6.1 LITERATURE ON COST-EFFECTIVENESS

To determine the clinical utility of proton therapy and make wise choices between the different technologies, economic evaluation is often applied. As new treatments are regularly introduced, and healthcare costs continue to increase, it's paramount to know if the benefits of new technologies are worth the extra cost. Proton radiation therapy offers clinical advantages through superior dose distribution, reducing the risk of normal tissue damage and increasing the chances of cure thanks to dose escalation. It is, however, a costly new technology that comes with a high initial capital cost and operating expense. Some model-based calculation and analytical literature looks into the cost-effectiveness of proton therapy.

In 2005, researchers of the Karolinska Institute and Stockholm Health Economics conducted a detailed assessment of the cost-effectiveness of proton radiation therapy. Four types of cancers – left-sided breast, prostate, head and neck, and childhood medulloblastoma – were purposely chosen to explore if proton therapy can be applied cost-effectively for routine treatments and clinical research. The clinical effectiveness that was measured included survival, such as life years gained and disease-specific adverse events avoided. A reduction of adverse events is associated with lower costs and an increase in health utility (a measure of quality of life). Based on literature, the authors made several assumptions about proton therapy's reduction of adverse events and gain in life quality in comparison with conventional radiation therapy. For example, proton therapy could reduce the risk of cardiac and pulmonary side effects of left-sided breast cancer; it would generate a mortality risk reduction of 24% and a 0.75 utility score in head and neck patients; children treated by proton radiation would have a risk reduction of 52% for subsequent cancer, 33% for cardiac and other death, 88% for hearing loss, hypothyroidism, growth hormone deficiency, IQ loss and osteoporosis.[22]

The researchers then applied the classic economic evaluation model, which takes the cost per Quality Adjusted Life Year (QALY) into the Markov cohort simulation model in order to reach the total accumulated lifetime costs and QALYs. The simulation model was programmed for each cancer type and simulated the course of life of individual patients from diagnosis until death, with different stages associated with certain costs and utility. The result in table 6.1 shows the average cost-effectiveness ratio of proton therapy for the four types of selected cancers to be about €10,130 ($11,400) per QALY gained. If a gained QALY was estimated at a value of €55,000 ($61,900), the total yearly net benefit added up to about €20.8 ($23.4) million in the study. The authors drew the conclusion that proton therapy may be a cost-effective treatment if it targets a selection of appropriate risk groups, and that the investment in a proton facility may be cost-effective compared to using conventional radiation.[22]

The authors do point out limitations of the study, recognizing that the assumptions are based on limited clinical and economic outcome data, as well as the comparison evaluation is not made with the most relevant alternatives, since long-term studies are unavoidably based on older technologies. In addition, there's the assumed 30-year lifetime of a proton therapy facility, while the potential introduction of new techniques and improvements could affect the validity of the assumptions.[22]

Three articles by Björk-Eriksson and Glimelius reiterated proton therapy's cost-effectiveness to treat head and neck, breast and pediatric cancers. The first article

Proton versus conventional therapy outcome					
	Breast cancer[1]	Prostate cancer	Head & neck cancer	Medullo-blastoma	Total
Number of patients per year	300	300	300	25	925
Δ Cost*	5920.0	7952.6	3887.2	-23 646.5	
Δ QALY*	0.1726	0.297	1.02	0.683	
Corst per QALY	34 290	26 776	3811	Cost saving	
Total cost difference (M€)**	1.8	2.4	1.2	-0.6	4.7
Total difference in QALYs**	51.8	89.1	306.0	17.1	464.0
[1] Assuming that a population at high risk of cardiac diseases is treated.					
* Per patient, proton - conventional radiation.					
** For all treated patients during one year.					

Table 6.1: Summary of proton cost-effectiveness breast, prostate, head and neck and medulloblastoma by Lundkvist et al[22]

evaluated cost-effectiveness for a 65-year-old man with hypopharyngeal cancer and came to the conclusion that proton treatment can reduce xerostomia and the risk of tumor death by 23%, resulting in a cost per QALY of approximately SEK35,000[23] (€3800/$4270) to be gained. The second article considered the case of a 55-year-old woman with left-sided breast cancer, post-operatively irradiated to 50Gy (RBE). It found proton therapy was able to reduce the risk of serious cardiac toxicity by 76% and of pneumonitis by 96%. According to the authors, the group of patients with the risk of cardiac toxicity exceeding 3% would gain a cost per QALY of SEK202,000 (€22,000/$24,650) with proton treatment.[24] The final article determined the use of proton treatment for a 5-year-old medulloblastoma patient as cost-effective based on the potentially reduced long-term toxicity compared to 3D CRT or IMRT.[25]

The proton-photon comparison in terms of cost-effectiveness in the management of pediatric medulloblastoma has again been reported in 2013 by the researchers at Washington University School of Medicine, St. Louis. A population of 18-year-old pediatric medulloblastoma survivors who had received radiation at the age of 5 was studied using a Monte Carlo simulation model. The conclusion associated proton therapy with higher QALY and lower costs. It dominated photon therapy in 96.4% of the simulations.[26]

Even though Japan preceded all others in clinically applying proton and carbon ion particle therapy, its pioneer cost-effectiveness study of proton radiation therapy was only published in early 2014. The study contained findings by researchers from Tokyo Medical University, Hokkaido University and Shizuoka Cancer Center and equally reported on childhood medulloblastoma. The researchers selected the cochlea as the organ at risk, focusing on hearing loss as the comparator between proton and photon treatment's cost-effectiveness. The Markov model was used on a cohort of patients receiving radiation at the age of six. Three health related quality-of-life indexes were chosen for utility-cost evaluation: EQ-5D, HUI3 and SF-6D. The incremental cost-effectiveness ratio (ICER) was calculated as the final index of the cost-utility analysis and the economic efficiency was evaluated based on the societal willingness-to-pay (WTP) value. The study used JPY 5 million (€37,050/$41,755) per QALY as the threshold standard. The authors agreed on the cost-effectiveness and societal affordability of proton therapy for medulloblastoma in children (as illustrated in table 6.2), but pointed out that its cost-effectiveness for other diseases such as lung, prostate and breast cancer needs further research to examine its economic effectiveness and medical utility.[27] Given the ever-increasing number of patients being treated with proton therapy in Japan, a large percentage of which have prostate cancer (30%), hepatocellular carcinoma (19%), head and neck (14%) and lung cancer (12%), new study results are likely to be reported in the near future (chart 6.1).[28]

In 2007, Konski et al. of the Fox Chase Cancer Center, Philadelphia, published a comparative cost-effective study between proton therapy and IMRT for prostate cancer. The study runs a Markov model at 15 years for a 70-year-old and a 60-year-old man. The incremental cost-effectiveness ratio was calculated to be $63,578 (€56,529) per QALY for the 70-year-old and $55,726 (€49,550) for the 60-year-old. Based on the common standard of $50,000 (€44,456) per QALY, the authors found proton therapy was not cost-effective for most patients with prostate cancer.[29]

A 2012 study by Parthan et al. compared the cost-effectiveness of stereotactic body radiation therapy (SBRT) versus IMRT and proton therapy (PT) for localized prostate cancer. The findings showed that SBRT was the least expensive option in terms of lifetime costs ($24,873) followed by IMRT ($33,068) and PT ($69,412) and offered the highest gain of QALYs, namely 8.11 versus 8.05 from IMRT and 8.06 from PT. The authors concluded that SBRT is cost-effective compared to IMRT and PT as it provides

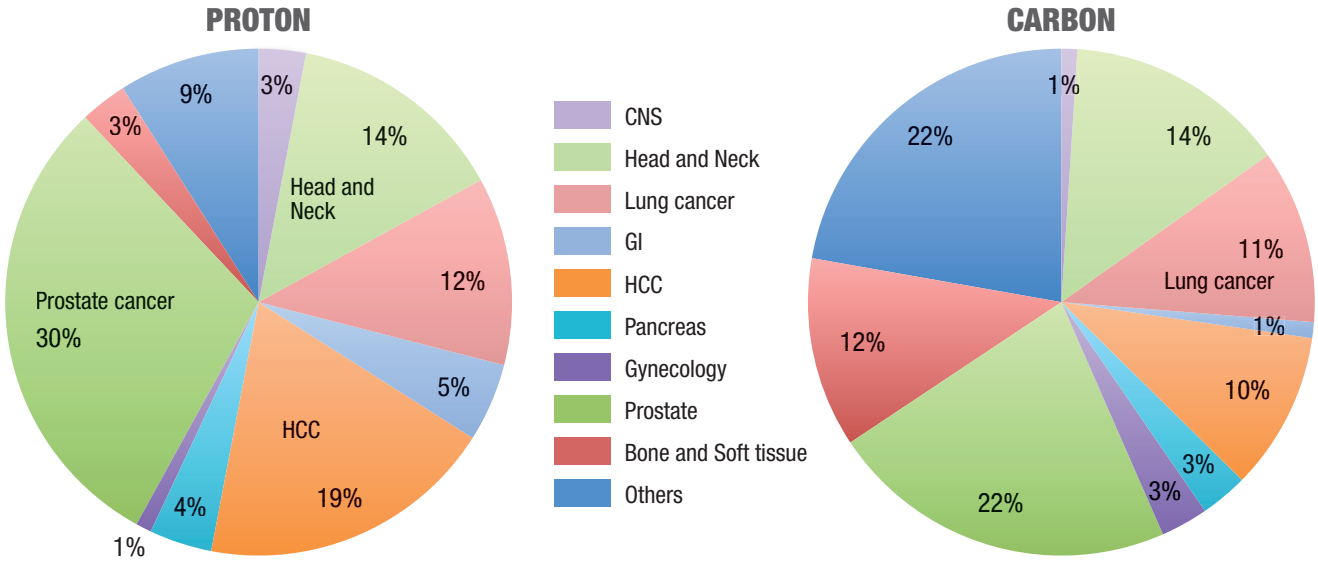

Chart 6.1: Patients statistics in Japan for Proton and Carbon from Tetsuo[28]

cost savings and improved quality-adjusted survival for the treatment of localized prostate cancer.[30]

Recently, a joint publication by researchers from renowned institutes in radiation oncology and health economics provided the first evidence-based guide for identifying children with CNS tumors for whom proton therapy may provide a cost-effectiveness benefit with respect to endocrine dysfunction. It suggests proton therapy may be more cost-effective for scenarios in which the radiation dose to the hypothalamus can be spared, but not cost-effective with regard to growth hormone deficiency (GHD) when proton plans deliver a high dose to this critical structure. Despite the high cost of proton therapy, averting the high cost of GHD alone can render proton therapy a cost-effective and even cost-saving strategy compared with photon therapy.[31]

The proof of proton therapy's cost-effectiveness is well-recognized for indications such as pediatric tumors, but remains uncertain for some adult cancers. Some leading experts pointed out that combinations of proton and IMRT may offer improved treatment plans at lower cost than pure proton plans. Hypofraction with proton therapy appears to be safe and cost-effective for many tumor sites, such as selected liver, lung and pancreas cancers, and may afford significant reduction in the cost of a therapy course.[31] In the absence of level-one evidence, well-performed modeling studies can help address the problem of limited outcome and health economic data. Lievens et al. proposed collecting ongoing evidence in order to allow technological advances with limited initial evidence of benefit and value, such as protons, to become available to patients in an early phase of the technology life cycle.[32]

Literature reviews on proton radiation therapy's cost-effectiveness using the classic economic evaluation model, which takes the cost per Quality Adjusted Life Year (QALY) into the Markov cohort simulation model, thus show that proton therapy may be a cost-effective treatment if appropriate risk groups are chosen as targets. Furthermore, an investment in a proton facility may be cost-effective compared to conventional radiation because of the reduction of adverse event and the gain in life quality that this therapy offers.

6.2 GOVERNMENT REPORTS ON COST-EFFECTIVENESS ASSESSMENT

The UK National Proton Beam Therapy Service Development Program made an in-depth assessment of the cost-effectiveness of proton treatment. An estimation about the improvement in outcomes to be expected from proton therapy compared to conventional radiation therapy was made based on a literature review as well as an expert panel. The analysis was performed using the Markov model in the Monte Carlo simulation. A list of 32 indications, including most pediatric tumors, adult brain, ocular, head and neck cancers, difficult cases and others, was used in the calculation of QALY gain.[14] The average QALY gain is presented in table 6.3.

Results of Markov model analysis by utility: per patient					
	Cost	QALY	ΔCost	ΔQALY	ICER (S/QALY)
EQ-5D					
proton therapy	$28 937.00	23.44	21 396	0.98	21 716
X-ray therapy	$7 541.00	22.46	…		
HUI3					
proton therapy	…	22.78	…	1.82	11 773
X-ray therapy	…	20.96	…		
SF-6D					
proton therapy	…	23.38	…	1.06	20 150
X-ray therapy	…	22.32	…		
QALY = quality adjusted life years, ICER = incremental cost-effectiveness ratio.					

Table 6.2: Cost and QALY for children medulloblastoma from Hirano[27]

In 2009, the UK National Radiation Therapy Advisory Group determined an immediate need for up to 400 high priority patients per annum to have access to proton treatment. Patients are currently referred overseas for treatment, but in many cases it is inappropriate to send them abroad due to the complex nature of their treatment or inability to travel. There is also significant disruption to the whole family. Furthermore, there is limited overseas proton capacity. The total cost of overseas referral, £110,000 (€149,815/$168,370), as shown in table 6.4, served as a comparative parameter in the calculation of the incremental cost effectiveness ratio. This in-depth evaluation of proton therapy's cost-effectiveness has resulted in the approval of two proton facilities in the UK.[14]

A recently published report on a study investigating the building of a hadron therapy center in Belgium presented the health economic evaluation of proton therapy for locally advanced, non-small cell lung cancer. Based on literature findings, it applied the Markov cost-utility analysis approach, took into account the cost of side-effect, local progression and distant progression probability and compared chemotherapy-combined 3D CRT, chemotherapy-combined IMRT and chemotherapy-combined proton therapy. The calculation results are shown in tables 6.5 and 6.6, and the report concludes that cost/QALY-wise, proton therapy turns out borderline cost-effective versus the current alternatives whereas the outcome is overall better for proton therapy when it comes to LY gains.[33]

QALY/patient	Radiotherapy		PBT		Difference (Gain from PBT)	
	High priority indications	All indications	High priority indications	All indications	High priority indications	All indications
Undiscounted	22.9	14.2	27.2	17.1	4.4	2.8
Discounted	14	9.4	16.5	11.2	2.5	1.8

Table 6.3: Average QALY gain per patient following treatment from the UK report[14]

The Netherlands proton radiation therapy horizon scanning report made a similar, highly detailed assessment of the cost-effectiveness of proton therapy. The results are positive, leading to the recommendation to have four proton facilities in the Netherlands and one combined proton and carbon ion center in Belgium.[8]

6.3 REIMBURSEMENT FOR PROTON TREATMENT

Reimbursement for proton treatment is a multifaceted issue. The reimbursement rates vary from €20,000 ($22,500) to €40,000 ($45,000), which is more or less in line with the treatment cost. Reimbursement systems tend to differ by country, but consistency can be found in the selection of tumors being covered as standard proton therapy indications. The UK even reimburses British patients who are referred for overseas treatments for well-defined indications, the cost of which adds up to about £110,000 (€149,815/$168,370).[14, 33]

Cost to foreign patients			
Country	Institution	Local reimbursement (Technical fees PT only)	Charge to foreigners
Switzerland	PSI	1,100 CHF/ fraction	30-40,000 €/ patient
France	Orsay	1,300 €/frac	40,000 €/pat
Germany	Essen, Munich	20k €/frac (German)	>50,000 €/pat (foreign)
USA	Loma Linda	1,200 $/frac (Medicare)	160,000 $/pat
USA	MD Anderson	1,200 $/frac (Medicare)	180,000 $/pat
USA	UPENN	1,200 $/frac (Medicare)	>100,000 $/pat
USA	UFPTI Florida	1,200 $/frac (Medicare)	>120,000 $/pat
USA	MGH	1,200 $/frac (Medicare)	>200,000 $/pat
USA	HUPTI Virginia	1,200 $/frac (Medicare)	>80,000 $/pat
USA	Procure	1,200 $/frac (Medicare)	>80,000 $/pat
Korea	KNCC		48,000 $/pat
Middle East	SAH		90,000 – 180,000 $/pat

Table 6.4: Proton therapy treatment cost charged to foreigners patient in various Proton Therapy Centers

In the United States, proton therapy can count on long-standing support from health insurers as the modality has been available for two decades. However, in recent years, proton reimbursement by Medicare has been volatile, a 15% increase in 2012 ($35,900/€31,500) having been followed by a decline of nearly 32% in 2013 ($24,500/€21,500 per patient).[34] Major private payers such as Blue Cross Blue Shield have changed their policies, categorizing proton treatments for prostate cancer, lung cancer, left breast tumors, liver and others as 'investigational'.[35] Nevertheless, the US reimbursement system is intricate, experts are at odds on the issue, and debate continues.

In the APAC region, Japan maintains a proton reimbursement rate of approximately JPY 3 million (€21,500/$24,500) per patient while South Korea counted an amount of KRW 492,350 (€365/$410) per fraction in 2012. An evaluation of local reimbursement options is advisable if there are plans for a proton project. When the government of countries such as the UK, the Netherlands and Belgium set up the approval process to establish local proton treatment facilities, it simultaneously assessed

Treatment-related toxicity occurrence (≥grade3)				
Treatment	Esophagitis	Pneumonitis	Fibrosis	Source
3D-CRT	31.6%	30%	8.3%	Mazeron et al. (2010) [30], Sejpal et al. (2011) [29]
IMRT	31.6%	9%	7.6%	Jiang et al. (2012) [31], Sejpal et al. (2011) [29]
Proton	5%	2%	4.5%	Chang et al. (2011) [31], Sejpal et al. (2011) [29]

Table 6.5: Treatment related toxicity for NSCL from the Belgium report[33]

Overview of the Markov model outputs expressed in cost/QALY					
Chemotherapy + 3D-CRT		Chemotherapy + proton			
QALYs	Cost (€)	QALYs	Cost (€)	delta QALY	delta cost (€)
1,408	31,200	1,957	50,075	0.549	18,875
ICER					34,396
Chemotherapy + IMRT		Chemotherapy + proton			
QALYs	Cost (€)	QALYs	Cost (€)	delta QALY	delta cost (€)
1,505	35,818	1,957	50,075	0.452	14,257
ICER					31,541

Overview of the Markov model outputs expressed in cost/LY gained					
Chemotherapy + 3D-CRT		Chemotherapy + proton			
LY	Cost (€)	LY	Cost (€)	delta LY	delta cost (€)
2,363	31,200	3,200	50,075	0.837	18,875
ICER					22,543
Chemotherapy + IMRT		Chemotherapy + proton			
LY	Cost (€)	LYs	Cost (€)	delta LY	delta cost (€)
2,536	35,818	3,200	50,075	0.664	14,257
ICER					21,469

Table 6.6: Treatment outputs expressed in Cost/QALY for NSCLC from the Belgium report[33]

reimbursement options for proton treatment based on a variety of data, like detailed financing, costing and patient treatment charges.

7. CURRENT PROTON THERAPY AVAILABILITY WORLDWIDE

The August 2015 update of the Particle Therapy Co-operative Group (PTCoG) website lists up 58 proton therapy centers in operation, 36 under construction and 14 in planning stage worldwide.

More than 50% of the proton centers treating patients are located in the United States (17 centers) and in major Western Europe countries (14 centers). Several facilities are soon to follow. In the USA, 15 more proton therapy facilities are expected to be treating patients by the end of 2017. The Netherlands will count two proton therapy centers by then, two others being planned for. In the course of 2015, a second facility opened its doors to patients in France, another one is expected to become operational in 2018. Austria will join the proton therapy community in 2016.

In Asia Pacific, Japan looks back on a long history of particle therapy. The country already has the highest number of proton therapy facilities in the region, and by the end of 2016, four more centers will join the 13 already in service today.
The first South Korean proton therapy center has been treating patients since 2007. It is part of the National Cancer Center, which has been publishing its work regularly and acts as the Principal Investigator on several clinical trials, including two randomized controlled studies on liver and prostate cancer. Samsung Medical Center,

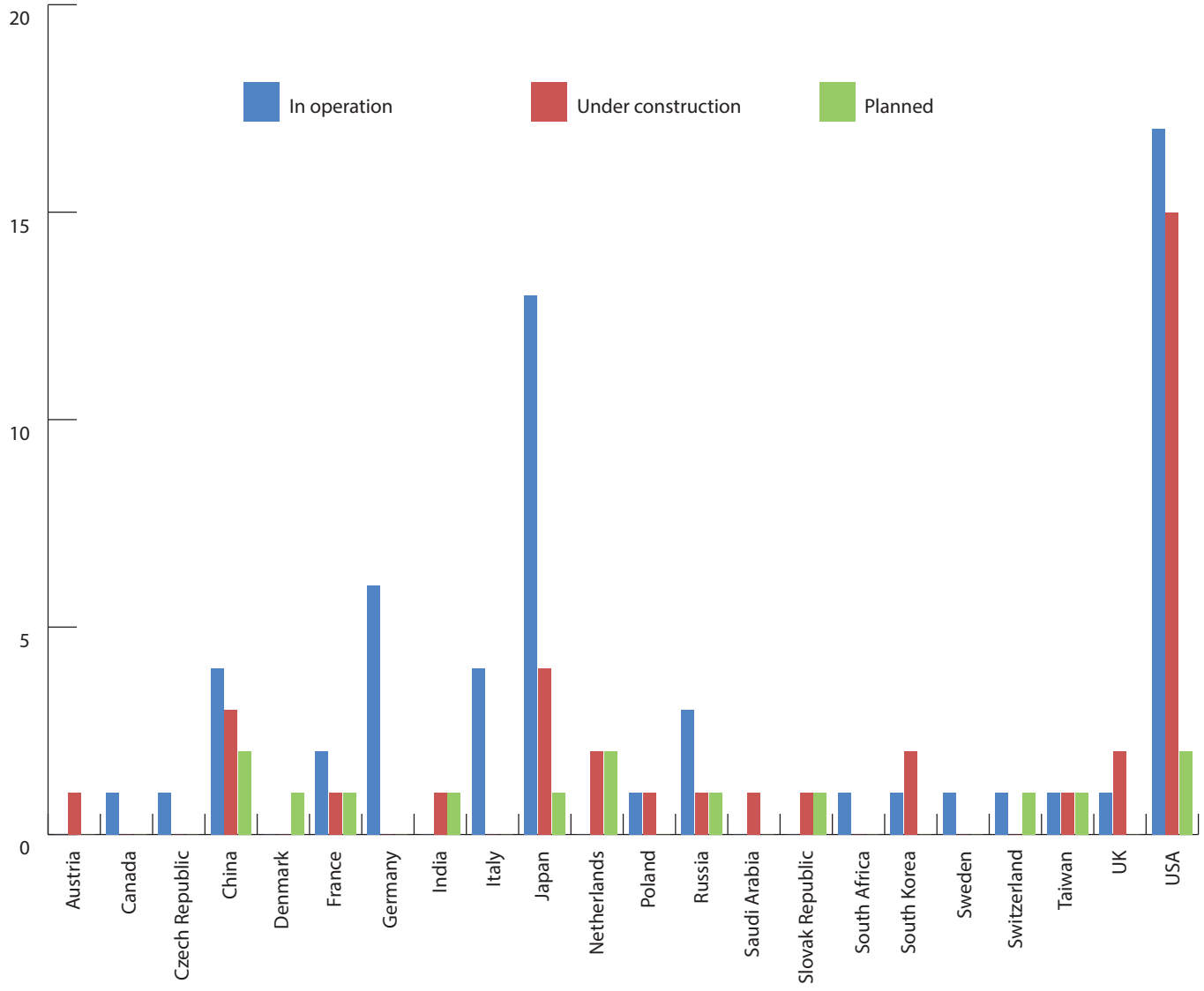

Chart 7.1: Number of Proton Therapy Centers in operation, construction and planning by country

Seoul, another leading research-based teaching hospital, is about to start treating patients and by 2018, South Koreans will have access to a third treatment facility.

China counts four operational proton therapy centers and will add five more by the end of 2019. Next in line are Taiwan, which has one proton therapy center, with another one under construction and a third one in a planning stage, and India, which has two facilities on the way.

Modern radiation oncology leverages on technological excellence, and proton therapy's installed base shows a worldwide trend of more and more institutions acquiring the technology. Many experts believe that proton therapy's accessibility will grow considerably in the very near future.

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