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Lung cancer staging: a concise update

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Lung cancer staging is a multidisciplinary activity that involves specialists in imaging, endoscopists, surgeons and pathologists at clinical and pathological staging <http://ow.ly/z3M030jzmhN>

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ABSTRACT Diagnosis and clinical staging of lung cancer are fundamental to planning therapy. The techniques for clinical staging, *i.e.* anatomic and metabolic imaging, endoscopies and minimally invasive surgical procedures, should be performed sequentially and with an increasing degree of invasiveness. Intraoperative staging, assessing the magnitude of the primary tumour, the involved structures, and the loco-regional lymphatic spread by means of systematic nodal dissection, is essential in order to achieve a complete resection. In resected tumours, pathological staging, with the systematic study of the resected specimens, is the strongest prognostic indicator and is essential to make further decisions on therapy. In the present decade, the guidelines on lung cancer staging of the American College of Chest Physicians and the European Society of Thoracic Surgeons are based on the best available evidence and are widely followed. Recent advances in the classification of the adenocarcinoma of the lung, with the definition of adenocarcinoma *in situ*, minimally invasive adenocarcinoma and lepidic predominant adenocarcinoma, and the publication of the eighth edition of the tumour, node and metastasis classification of lung cancer, have to be integrated into the staging process. The present review complements the latest guidelines on lung cancer staging by providing an update of all these issues.

Previous articles in this series: **No. 1:** Malhotra J, Malvezzi M, Negri E, *et al.* Risk factors for lung cancer worldwide. *Eur Respir J* 2016; 48: 889–902. **No. 2:** McDonald F, De Waele M, Hendriks LEL, *et al.* Management of stage I and II nonsmall cell lung cancer. *Eur Respir J* 2017; 49: 1600764. **No. 3:** Leduc C, Antoni D, Charloux A, *et al.* Comorbidities in the management of patients with lung cancer. *Eur Respir J* 2017; 49: 1601721. **No. 4:** Zugazagoitia J, Molina-Pinelo S, Lopez-Rios F, *et al.* Biological therapies in nonsmall cell lung cancer. *Eur Respir J* 2017; 49: 1601520. **No. 5:** Calvayrac O, Pradines A, Pons E, *et al.* Molecular biomarkers for lung adenocarcinoma. *Eur Respir J* 2017; 49: 1601734. **No. 6:** Meert A-P, Grigoriu B, Licker M, *et al.* Intensive care in thoracic oncology. *Eur Respir J* 2017; 49: 1602189. **No. 7:** Glatzer M, Rittmeyer A, Müller J, *et al.* Treatment of limited disease small cell lung cancer: the multidisciplinary team. *Eur Respir J* 2017; 50: 1700422. **No. 8:** Peeters-Asdourian C, Massard G, Rana PH, *et al.* Pain control in thoracic oncology. *Eur Respir J* 2017; 50: 1700611.

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Introduction

The thoracic oncology community worldwide has never had such solid clinical practice guidelines on lung cancer staging as the ones provided by the American College of Chest Physicians and the European Society of Thoracic Surgeons (ESTS) in this decade [1–3]. Well-researched and profusely documented, these guidelines have set the pace of lung cancer staging in most parts of the world. They emphasise the importance of achieving the highest possible certainty at clinical and pathological staging by the thoughtful combination of imaging, endoscopies, minimally invasive surgical procedures, and thorough intraoperative staging, as well as by a sound pathological examination of tissue biopsies, fluids and resected specimens. Ideally the different tests available should be performed sequentially and with an increasing degree of invasiveness. Staging at the time of diagnosis is fundamental to planning initial therapy, and staging after tumour resection is the strongest prognostic indicator and provides information essential for making decisions on postoperative therapy.

In 2015, the new classification of adenocarcinoma of the lung, proposed by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society and the European Respiratory Society in 2011 [4], was accepted by the World Health Organization and included in its most recent book on pathology of thoracic malignancies [5].

A year later, the eighth edition of the tumour, node and metastasis (TNM) classification was published jointly by the Union for International Cancer Control (UICC), the American Joint Committee on Cancer and the IASLC [6–8]. The new primary tumour categories based on tumour size [9]; the coding for adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA), and the recommendation on how to measure tumour size [10]; the reclassification of some T descriptors [9]; the relevance of quantifying nodal disease [11]; the subclassification of extrathoracic metastases [12]; and the rearrangement of stage groupings [13] have staging and clinical implications that will have to be addressed by all those involved in the management of lung cancer patients (tables 1 and 2).

It is in the context of these events that this concise review, authored by an international and multidisciplinary team of professionals deeply involved in lung cancer staging, is offered with the objective to update relevant issues that complement the published guidelines.

Imaging techniques

Radiology and nuclear medicine play an important role in the clinical staging of lung cancer. After a proper medical history and physical examination, chest radiography usually is the first step in the study of many thoracic diseases [14], but contrast-enhanced spiral computed tomography (CT) is the technique of choice in the study of lung cancer [15]. CT should examine the chest and the upper abdomen. Chest radiography is useful for the assessment of the postoperative course on a day-to-day basis, and for postoperative follow-up, as a baseline to compare with subsequent radiographic studies. Positron emission tomography (PET) imaging, and especially the integrated PET-CT technique, have changed the staging of lung cancer, and should be routinely performed for optimal clinical staging. Other techniques, such as transthoracic ultrasounds or magnetic resonance imaging (MRI), play a secondary role with specific indications.

The T component

CT remains the best technique in the clinical measurement of tumour size [16]. The size of the tumour is one of the most important prognostic factors in lung cancer. In the eighth edition of the TNM classification, it proved to be more relevant than in the previous editions, because it can separate tumours of significantly different survival at 1 cm intervals from less than 1 cm to 5 cm in greatest dimension [9]. In clinical staging, tumour size should be measured with inspiratory CT using the lung window, and the longest diameter in any projection should be reported [10]. In cases of part-solid pulmonary nodules with ground glass opacity, the size of the solid component is the one to be used to assign a clinical T category based on size [10]. It is also recommended to register the total size (solid and ground glass components) to evaluate its prognostic implications, because presence of a ground glass component has a favourable prognosis [17]. The CT findings of ground glass and solid opacities in non-mucinous adenocarcinomas tend to correspond with lepidid and invasive histopathological patterns, respectively. These radiographic findings suggest the diagnosis of AIS, MIA or lepidid predominant adenocarcinomas (LPA), but the correlation is not absolute and should be regarded as a preliminary assessment subject to revision after histopathological evaluation of the resected specimens [10].

In general, CT depicts the invasion of the great vessels or mediastinal structures, but other techniques are useful in specific settings. Transthoracic ultrasound and MRI offer better results than CT in the evaluation of parietal pleural and chest wall invasion [18, 19]. For pre-operative staging of Pancoast tumours MRI

TABLE 1 Main innovations in the eighth edition of the TNM classification of lung cancer

Parameter	Innovation
T descriptors	
Adenocarcinoma <i>in situ</i>	Tis (AIS)
Minimally invasive adenocarcinoma	T1mi
Tumour ≤1 cm	T1a
Tumour >1 cm but ≤2 cm in greatest dimension	T1b
Tumour >2 cm but ≤3 cm in greatest dimension	T1c
Tumour >3 cm but ≤4 cm in greatest dimension	T2a
Tumour >4 cm but ≤5 cm in greatest dimension	T2b
Tumour >5 cm but ≤7 cm in greatest dimension	T3
Tumour >7 cm in greatest dimension	T4
Endobronchial location any distance from the main carina but with no invasion of the carina	T2
Total (whole lung) atelectasis or pneumonitis	T2
Invasion of diaphragm	T4
Invasion of mediastinal pleura	Disappears as a T descriptor
N descriptors	
Involvement of one N1 nodal station	N1a
Involvement of multiple N1 nodal stations	N1b
Involvement of one N2 nodal station without N1	N2a1
Involvement of multiple N2 nodal stations with N1	N2a2
Involvement of multiple N2 nodal stations	N2b
M descriptors	
Single extrathoracic metastasis [#]	M1b
Multiple extrathoracic metastases in one or in several organs [#]	M1c
Measurement of tumour size	
On computed tomography	Use the lung window in the projection that provides the greatest dimension
Of part-solid tumours on computed tomography	Use size of solid component to assign a T category based on tumour size
Of part-solid non-mucinous adenocarcinoma at pathological examination	Use size of invasive component to assign a T category based on tumour size
After induction therapy	Multiply the percentage of viable tumour cells by the size of the total mass

[#]: this includes the involvement of non-regional lymph nodes.

showed better results than CT [20]. Transthoracic ultrasound, MRI and PET-CT might be of added value in the differentiation between lung cancer and obstructive atelectasis [16].

The N component

In 2009, the IASLC proposed a new chart of the regional lymph nodes, grouped in zones and stations [21] that has to be considered carefully in the staging of lung cancer [22]. A survey by EL-SHERIEF *et al.* [23] demonstrated that the use of older maps and the inconsistencies in interpretation and application of the definitions of the IASLC lymph node map may potentially lead to stage misclassification and suboptimal management of lung cancer in some patients. Classically, lymph nodes with a short axis over 10 mm measured by CT are considered abnormal. This classical criterion has little diagnostic accuracy [24]. In the diagnosis of nodal involvement, SHIM *et al.* [25] demonstrated a sensitivity of 0.70 for CT and of 0.85 for PET-CT. In addition, PRENZEL *et al.* [26] showed that 77% of patients without nodal involvement had nodes >1 cm in short axis, and that 12% of patients with N1 or N2 tumours did not present any node with a short axis >1 cm. PET-CT shows better results than CT alone and PET alone in the diagnosis of lymph node involvement [24–28]. Still, the sensitivity of PET-CT is related to the size of the nodes, with a sensitivity of 0.85 for nodes greater than or equal to 10 mm, but of only 0.32 for nodes less than 10 mm in diameter [29].

Diffusion-weighted MRI has a potential role to differentiate benign from malignant lymph nodes [30]. A meta-analysis performed by WU *et al.* [31] demonstrated that diffusion MRI has equal sensitivity than PET-CT (0.75 versus 0.72, respectively), but higher specificity (PET-CT 0.89 versus MRI 0.95). However, two clinical trials did not find differences in the diagnostic value of PET-CT and diffusion MRI for staging lung cancer [32, 33]. Diffusion-weighted MRI could be considered in some cases as an alternative to

TABLE 2 Stage grouping of the eighth edition of the TNM classification of lung cancer

Stage	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a, b, c	N1	M0
	T2a, b	N1	M0
	T3	N0	M0
IIIA	T1a, b, c	N2	M0
	T2a, b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a, b, c	N3	M0
	T2a, b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

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PET-CT [34], but more studies are needed to establish the role of MRI in the study of the N descriptors in lung cancer.

The M component

Lung cancer metastases can be intra- or extrathoracic. Lung metastases can be identified on CT. The eighth edition of the TNM classification provides recommendations on how to differentiate separate tumour nodules from multifocal adenocarcinomas at clinical and pathological staging [35, 36]. CT can identify pleural metastasis as pleural nodules, and PET-CT can show pleural uptake of FDG [16]. Extrathoracic metastases can be depicted easily with PET-CT. One of the important contributions of PET-CT for lung cancer staging is the detection of unrecognised metastases and upstaging of tumours [37]. Adrenal metastases can be correctly depicted by PET-CT [38, 39], and no other techniques are needed. In a systematic review and meta-analysis of published data, PET alone showed a sensitivity of 0.97 and a specificity of 0.91, with a false-positive rate of 9.7%, due to some benign adrenal lesions that showed mild FDG uptake [40]. Therefore, isolated positive adrenal lesions should be confirmed in order to avoid deeming a patient inoperable on a false-positive basis [37]. Cerebral staging is recommended in all patients with curative therapeutic options [41, 42]. MRI shows better results than CT in the diagnosis of brain metastases [43]. DEUSCHL *et al.* [44] evaluated PET-MRI performed in lung cancer staging, concluding that PET-MRI did not show any improvement in cerebral staging of these patients, as MRI alone remains the gold standard. Nevertheless, brain imaging is not necessary in the staging of pure ground glass nodular lung adenocarcinoma [45]. Bone metastases can be detected with PET-CT, PET-MRI and diffusion sequence in MRI [37].

Globally, PET-CT is the best tool in the initial staging of lung cancer, even in the study of small cell lung cancer [46], compared with CT, bone scan and bone marrow analysis [16, 47], except for brain metastases.

New techniques

PET-MRI is a promising hybrid technique combining anatomy and functional imaging. USUDA *et al.* [48] did not find significant differences in accuracy between staging tumours with PET-CT plus brain MRI and whole-body diffusion-weighted MRI, and concluded that they were equivalent in the staging of clinically resectable lung cancer. Combining PET-MRI with or without contrast-enhanced CT is comparable to

PET-CT in the preoperative staging of lung cancer [49, 50], with a reduction of 31% of the radiation dose [50]. Another study comparing coregistered whole-body MRI-PET with PET-CT plus brain MRI found that both staging protocols had greater than 20% correct upstaging compared to conventional staging methods, but MRI-PET was not superior to PET-CT plus brain MRI [51].

New radiotracers, such as ^{18}F -fluorothymidine, ^{11}C -methionine, ^{18}F -fluoromisonidazole, and ^{68}Ga -DOTA-peptides, have been used in a research environment but could have an important role in the next few years in the era of personalised therapy for patients with lung cancer [52]. In fact, ^{68}Ga -DOTA-peptide scan already is part of the standard staging work-up in cases of FDG-negative (a)typical carcinoid. In a study of 53 patients, ^{18}F -NaF PET showed no false-negatives in the detection of bone metastases, while bone scan and SPECT had six and one false-negatives, respectively [53]. Also, ^{18}F -NaF PET impacted the clinical management in 11% of the patients [53].

Endoscopic techniques

Standard flexible videobronchoscopy for lung cancer staging

White light flexible videobronchoscopy permits endobronchial staging of the primary tumour in addition to pathological confirmation. A flexible bronchoscopy can determine the endobronchial extension of the primary tumour (T1a, radio-occult superficial spreading tumour of any size with its invasive component limited to the bronchial wall which may extend proximal into the main bronchus; T1, tumour ≤ 3 cm not extending into main bronchus; T2, tumour involving main bronchus distal to main carina; T4, tumour involving main carina and/or distal trachea), or can detect synchronous radio-occult endobronchial lesions [9]. In addition, a conventional transbronchial needle aspiration can be performed during the initial flexible bronchoscopy if enlarged mediastinal lymph nodes are present on computed tomography of the chest. In clinical N2 disease with a prevalence of N2/N3 disease of $>80\%$ the technique has a variable sensitivity of 0.15–0.83 to detect nodal disease and a false-negative rate of 28%, mostly related to the size and location of the nodes and the operators' experience [54, 55]. Nevertheless, as demonstrated within a randomised controlled trial, a conventional transbronchial needle aspiration (TBNA) performed during a first standard bronchoscopy can be a valuable mediastinal staging tool in clearly enlarged (defined as >15 mm in largest short axis) nodes in stations 4R (right inferior paratracheal), 7 (subcarinal) and 4L (left inferior paratracheal), or for unresectable bulky mediastinal nodal infiltration when a pathological diagnosis is lacking [56].

Linear endosonography for mediastinal lymph node staging in non-small cell lung cancer

When mediastinal nodal staging by linear endobronchial ultrasonography with transbronchial needle aspiration (EBUS-TBNA) is required, systematic nodal sampling seems feasible but some primary choices have to be made. At least mediastinal nodal stations 4R (right inferior paratracheal), 4L (left inferior paratracheal) and 7 (subcarinal) should be sought. All FDG-PET positive node(s) or the largest node ≥ 5 mm in each nodal station should be biopsied. It is possible to visualise and sample lymph nodes with a short axis of ≥ 5 mm and the optimal number of aspirations per station for nodal staging has been reported to be three [57, 58]. To avoid contamination, the order of sampling should begin at the level of N3 stations followed by N2 stations before N1 stations.

EBUS allows the exploration of mediastinal lymph node stations 2R (right superior paratracheal), 2L (left superior paratracheal), 3p (retrotracheal), 4L (left inferior paratracheal), 4R (right inferior paratracheal) and 7 (subcarinal). It must be stressed that EBUS cannot access the prevascular nodes (station 3a), the subaortic and para-aortic nodes (stations 5 and 6), or the para-oesophageal and pulmonary ligament nodes (stations 8 and 9). Some of these nodes (stations 8 and 9) can, however, be reached from the oesophagus. Several authors have therefore extended the use of the EBUS scope to an oesophageal exploration (EUS-B) of stations 4L (left inferior paratracheal), 7 (subcarinal), 8 (para-oesophageal) and 9 (pulmonary ligament) [59, 60].

Linear endosonography is a safe procedure with a low complication rate of 1–2% and reported mortality of 0.01% [61, 62].

Endosonography for mediastinal/hilar nodal staging in early stage non-small cell lung cancer

In patients with tumours classified as clinical N0 at PET-CT, recent studies reported a risk of mediastinal nodal involvement of $<20\%$ and sensitivity of 0.17–0.41 for EBUS-TBNA to detect mediastinal nodal disease [63–66]. Two prospective multicentre studies reported a risk of mediastinal nodal involvement of 25% in 205 patients classified as clinical N1 at PET-CT [67, 68]. In resectable patients classified as clinical N1 at PET-CT, a sensitivity of 0.38–0.53 has been reported for endosonography to detect mediastinal nodal disease [66, 67, 69].

Overall, the routine use of a preoperative EBUS-TBNA for systematic mediastinal nodal sampling in clinical stage I–IIB non-small cell lung cancer has only a moderate sensitivity to detect mediastinal nodal disease and does not greatly increase the negative predictive value of PET-CT [63–68]. In the concepts of Bayesian decision analysis, given a pre-test prevalence of 10–25% and sensitivity for EBUS-TBNA of less than 50% to detect mediastinal nodal disease in early stage non-small cell lung cancer, a post-test probability of greater than 10% is expected requiring another invasive staging test, taking into account the testing decision threshold of 10% required by the ESTS guidelines [2]. Therefore, the routine use of EBUS-TBNA for mediastinal nodal staging in clinical stage I–IIB lung cancer should not be offered, but a mediastinoscopy may represent the preferred approach in invasive mediastinal nodal staging in these patients.

It should be acknowledged, however, that EBUS-TBNA can accurately assess the hilar and interlobar lymph nodes in clinical N1 disease with a sensitivity and negative predictive value of 0.76 and 0.96, respectively [69]. The latter is relevant to non-surgical patients considered for stereotactic body or conformal radiotherapy.

Endosonography for mediastinal nodal staging in locally advanced non-small cell lung cancer

A risk of mediastinal nodal involvement of at least 60% has been reported in patients with tumours classified as clinical N2/3 at PET-CT. The two staging strategies proposed in the 2007 ESTS guidelines, surgical staging alone on the one hand and endosonography followed by surgical staging whenever endosonography was negative on the other hand, were compared in a pivotal randomised controlled trial [70, 71]. It was concluded that invasive mediastinal nodal staging should start with endosonography, as the trial showed that a staging strategy starting with combined linear endosonography detected significantly ($p=0.02$) more mediastinal nodal disease compared to cervical mediastinoscopy alone, resulting in a significantly higher sensitivity of 0.94 (95% CI 0.85–0.98) compared to 0.79 (95% CI 0.66–0.88), respectively [71]. A subgroup analysis of patients with clinical N2/3 at PET-CT demonstrated a sensitivity for endosonography of 0.86 to detect N2/3 disease, which increased to 0.97 when surgical staging was added after a negative endosonography [72]. Another randomised controlled trial comparing EBUS-TBNA with cervical mediastinoscopy in a patient group with 59% mediastinal nodal disease demonstrated a sensitivity of 0.88 (95% CI 0.78–0.94) and 0.81 (95% CI 0.70–0.89), respectively, confirming endosonography to be the first choice in invasive mediastinal staging for clinical N2/3 lung cancer [73]. Given a post-test probability after a negative test of >0.10 for endosonography in a context of high index of suspicion for mediastinal nodal disease, a confirmatory cervical mediastinoscopy is warranted as this lowers the post-test probability to <0.05 [2, 72–74]. In case of a positive result by EBUS-EUS demonstrating N2 disease, mediastinoscopy can be performed after induction therapy to evaluate tumour response and decide on further treatment. This strategy yields the highest sensitivity and accuracy in restaging after induction therapy [75].

Combined endobronchial and oesophageal endosonography

There has been no randomised controlled trial comparing combined EBUS and EUS-B to EBUS-TBNA alone for mediastinal nodal staging, but a recent meta-analysis assessed the accuracy and the added value of the combined use of endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer [74]. The mean sensitivity and negative predictive value of the combined approach in studies that relied on a reference standard with low risk of bias were 0.83 (95% CI 0.77–0.87) and 0.91 (95% CI 0.86–0.95), respectively [74]. The addition of EUS(-B) to EBUS led to a mean increase in sensitivity of 0.12 (95% CI 0.08–0.18) and to a mean increase in detection rate of 0.04 (95% CI 0.03–0.06), which implies a number needed to test of 25 (95% CI 17–33) to detect one additional patient with mediastinal nodal metastases that would be missed if only EBUS-TBNA had been done [74]. Although not yet widely adopted, combined EBUS and EUS-B can be done both with the EBUS scope in conjunction in a single session by a single endoscopist. This strategy facilitates the combined endobronchial and oesophageal endosonography approach as this is quicker, more comfortable for patients and cost-effective compared to using two scopes by two endoscopists, reducing the need for surgical staging procedures [74–77].

Imaging guided (ultrasound/CT) transthoracic techniques

Transthoracic needle aspiration and transthoracic needle core biopsy

Transthoracic needle aspiration (TTNA) is usually performed to obtain tissue diagnosis of parenchymal nodules or masses. For this indication, an accuracy of 0.9 has been described, although it may decrease depending on the location, depth and size of nodules [78]. As a staging procedure, it can be useful in patients with contralateral nodules to confirm metastatic disease. For mediastinal staging, TTNA can be used when there is bulky mediastinal disease, to diagnose and certify its extension. In this situation, a sensibility of 0.94 has been reported, with an average prevalence of mediastinal cancer $>80\%$. For the

diagnosis of peripheral lung lesions, transthoracic needle core biopsy (TNCB) compared with TTNA has similar sensitivity for malignancy but a better ability to determine a specific diagnosis for nonmalignant lesions. The main advantage of TNCBs is that they result in a higher yield of tissue specimens for mutation analysis [79]. Complication rate of both techniques is low, being the pneumothorax the most frequent (7–10%) [1, 79, 80].

Thoracentesis

Patients with suspected lung cancer presenting with pleural effusion should undergo thoracentesis with cyto-pathological analysis. Confirmation of malignant pleural effusion (MPE) is a sign of intrathoracic dissemination, defining an M1a category [12]. More than 90% of MPE are exudates and half of them haemorrhagic. Diagnostic yield ranges from 61% to 90% [79, 81, 82]. When two consecutive cytological examinations are negative, a video-assisted thoracoscopic surgery (VATS) is recommended due to its sensitivity >0.90 and low rate of complications [79, 81, 83].

Preoperative minimally invasive surgical staging techniques

Video-assisted thoracoscopic surgery

VATS allows the assessment of the T, the N and the M descriptors. Regarding those patients with lung cancer and several nodules in the same or contralateral lung, VATS can diagnose synchronous lung cancer *versus* T3 (separate tumour nodule(s) in the same lobe), T4 (separate tumour nodule(s) in a different ipsilateral lobe), or M1a (separate tumour nodule(s) in contralateral lung) [9, 12, 84]. Small nodules, especially those not involving the pleural surface, and subsolid ground glass opacities may be difficult to localise by VATS. Several techniques have been developed to facilitate their intraoperative detection [85]. When applying these targeting methods, the success rate of identifying nodules by VATS ranges from 96 to 99% [86].

The suspicion of pleural or pericardial effusion (M1a) can be pathologically confirmed by this technique, achieving a definitive diagnosis rate in 90–95% of cases. Moreover, chemical pleurodesis or pericardial window can be performed in the same procedure [80, 87–89].

VATS for mediastinal staging allows the assessment of ipsilateral lymph nodes. Regarding left-sided tumours, the aorto-pulmonary window lymph nodes can be easily explored; however, left paratracheal nodes usually remain unexplored due to their difficult access. Staging values of VATS show a sensitivity ranging from 0.58–1 (median 0.99) (table 3) and a false-negative rate of 4%. Average complication rate for this indication is 2% [1, 90–92].

TABLE 3 Accuracy of video-assisted thoracic surgery (VATS), videomediastinoscopy (VAM) and extended cervical mediastinoscopy (ECM) for surgical staging of the mediastinum in patients with lung cancer

Author	Year	Patients n	Prevalence %	Sensitivity	Specificity	PPV	NPV	Lymph node reached
VATS								
CERFOLIO [90]	2007	39	92	1	1	1	1	Left side: 5, 6, 7, 8L, 9L
MASSONE [91]	2003	55	55	1	1	1	1	Right side: 4R, 7, 8L, 9L
SEBASTIAN-QUETLAS [92]	2003	79	24	0.58	1	1	0.88	
VAM								
DECLAUWÉ [68] [¶]	2017	105	26	0.73	1	1	0.92	2R, 2L, 4R, 4L, 7, 8R, 8L
WEI [101]	2014	1240 [#]	46	0.90	1	1	0.92	
SAYAR [102]	2011	104	29	0.90	1	1	0.96	
ANRAKU [103]	2010	89	22	0.95	1	1	0.99	
LESCHBER [104]	2008	119	17	NA	1	NA	0.83	
KIMURA [105]	2007	209	31	0.78	1	1	0.91	
LARDINOIS [75]	2003	195	34	0.87	1	1	0.92	
VENISSAC [106]	2003	154	71	0.97	1	1	0.94	
ECM								
WITTE [107]	2013	92	21	0.94	1	1	0.96	5, 6
OBIOLS [108]	2012	221	15	0.68	1	1	0.94	
METIN [109]	2011	55	24	0.69	1	1	0.89	
FREIXINET [110]	2000	93	34	0.81	1	1	0.91	
GINSBERG [111]	1987	100	29	0.71	1	1	0.89	

PPV: positive predictive value; NPV: negative predictive value; NA: not available. [#]: the authors report 997 conventional mediastinoscopies and 243 VAM. Staging values were calculated based on the total number. [¶]: study in the context of clinical N1 disease.

Finally, VATS has also been described as an exploratory procedure to evaluate resectability and staging in order to decide proceeding to pulmonary resection in the same surgical act [93].

Pericardioscopy

In patients with pericardial effusion but without pleural effusion, there is no need to access the pericardium through the pleural space. In these cases, a subxyphoid approach provides access to the pericardium. It can be incised and the fluid drained. An endoscope, usually a mediastinoscope [94, 95] or a flexible endoscope [96], can be inserted to explore the inner surface of the pericardium and the epicardium. Biopsies can be taken and, if malignancy is proved, instillation of chemical agents for pericardiodesis can be done at the end of the procedure [96]. Pericardioscopy can also be useful to assess resectability of hilar tumours with suspicion of intrapericardial extension [97]. Sensitivity of pericardioscopy can be as high as 0.97. Complication rate is 6.1%, arrhythmias being the most frequent. Postoperative mortality of 3.5% has been reported, but it is important to consider that this procedure is usually performed in fragile patients with an advanced cancer [93, 95–99].

Mediastinoscopy and its variants

Based on the current North American and European guidelines for preoperative mediastinal nodal staging for lung cancer [1, 2], invasive methods are recommended to obtain tissue confirmation of regional nodal spread except in patients with small (≤ 3 cm) peripheral carcinomas with no evidence of nodal involvement on CT and PET. Minimally invasive endoscopic techniques (EBUS-TBNA and EUS-FNA or their combination) are included in the staging algorithms as the first invasive technique, when they are available. However, their negative results should be validated by surgical methods. To date, mediastinoscopy remains the gold standard in the staging process. It provides reliable information on the mediastinal nodal status and/or direct mediastinal invasion of the primary tumour.

Mediastinoscopy allows the exploration of the superior and middle mediastinum through a cervical incision. The use of a videomediastinoscope (VAM) over a standard mediastinoscope improves the visualisation of the operative field, which may increase accuracy and facilitate the teaching process [1, 100]. The nodal stations that can be reached are: right and left superior and inferior paratracheal (2R, 2L, 4R, 4L), subcarinal (7), right and left para-oesophageal (8R, 8L) and right and left hilar (10R, 10L) stations. According to European and North American guidelines, ideally, stations 2R, 2L, 4R, 4L and 7 should be examined routinely [1, 2]. Staging values described for VAM are: sensitivity ranging from 0.78 to 0.97, and negative predictive value ranging from 0.83 to 0.99 (table 3). Complication rate is 2%, temporal left recurrent laryngeal nerve palsy being the most frequent [1, 101–106].

Anterior mediastinotomy (the classic Chamberlain procedure) consists of a left parasternal incision at the level of the second or third intercostal space, to access the aortopulmonary window lymph nodes. The median sensitivity and negative predictive values reported are 0.71 and 0.91, respectively [1].

Extended cervical mediastinoscopy allows the assessment of subaortic (5) and para-aortic (6) stations from the same cervical incision used in the VAM. The exploration starts with a VAM, which rules out mediastinal involvement in paratracheal and subcarinal stations. A median sensitivity of 0.71 and negative predictive value of 0.91 have been described (table 3). Complication rate ranges from 0 to 7.2%, although the majority of them are not specific to extended cervical mediastinoscopy [1, 107–111].

Mediastino-thoracoscopy achieves the assessment of the mediastinum and pleural cavity using the transcervical approach [112]. At the time of mediastinoscopy, the mediastinal pleura can be opened and the pleural space, explored. The following procedures can be performed through this approach: aspiration of pleural fluid, pleural biopsies, resection of pulmonary nodules and/or instillation of pleurodesis agents. A pathological diagnosis is obtained in 78% of malignant lesions. Reported complication rate ranges between 0.7–10%, being the left recurrent laryngeal nerve palsy the most frequent [112].

Transcervical lymphadenectomies

Two new surgical staging procedures have been recently developed: video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA). In comparison with mediastinoscopy, in which only biopsy samples from lymph nodes are taken, these techniques achieve a complete clearance of all the lymph node stations explored, allowing the identification of minimal nodal disease that is not identified on CT or PET. The main difference between these procedures is that VAMLA is an endoscopic technique performed through a videomediastinoscope, and TEMLA is an open procedure assisted by a videomediastinoscope or a videothoracoscope, depending on the nodal station dissected. Due to their high diagnostic accuracy (table 4), VAMLA and TEMLA are especially indicated in those situations of intermediate probability of finding N2 disease: central tumours, clinical N1 tumours and tumour size >3 cm. Regarding complications, published series describe a

TABLE 4 Accuracy of transcervical lymphadenectomies for surgical staging of the mediastinum in patients with lung cancer

Author	Year	Patients n	Prevalence %	Sensitivity	Specificity	PPV	NPV	Lymph node reached
VAMLA								
CALL [113]	2016	151	18	0.96	1	1	0.99	2R, 2L, 4R, 4L, 7, 8R, 8L
TURNER [114]	2013	89	44	0.95	1	1	0.94	
WITTE [115]	2006	144	12	0.88	1	1	0.98	
TEMLA								
ZIELINSKI [116]	2014	928	25	0.96	1	1	0.98	1, 2R, 2L, 4R, 4L, 7, 8, 3a, 3p, 5, 6

PPV: positive predictive value; NPV: negative predictive value; VAMLA: video-assisted mediastinoscopic lymphadenectomy; TEMLA: transcervical extended mediastinal lymphadenectomy.

morbidity rate ranging from 4% to 9% for VAMLA and 6.6% for TEMLA. The most common complication for both procedures is recurrent laryngeal nerve palsy. Other infrequent complications are: pleural effusion managed with conservative treatment (1.6% for TEMLA), pneumothorax (0.4% for TEMLA, 0.5% for VAMLA), and postoperative bleeding requiring revision (0.2% for TEMLA, 0.5% for VAMLA). Regarding mortality, there was no mortality after VAMLA, and 5 (0.7%) patients died after TEMLA, but their deaths were unrelated to the procedure [113–117].

Intrathoracic staging at pulmonary resection

Whether lung resection is attempted by the classic thoracotomy approach or by any of the varieties (multiportal, uniportal, robotic) of VATS, it must ensure that the primary tumour is completely removed or that, if resection is not possible, adequate biopsies are taken to evaluate the highest pathological (p) T category [118]. During the operation, the primary tumour must not be transgressed and the adjacent or invaded structures, such as the chest wall, the diaphragm or the neighbouring lobe, must be resected *en bloc* to avoid spillage of cancer cells into the operative field [119]. If pleural effusion is identified on opening the chest, a sample should be taken for cytological analysis. Its positivity would classify the tumour as M1a. In case of diffuse pleural spread, lung resection will not improve prognosis.

Resection of the primary tumour must be accompanied by an adequate lymph node evaluation to validate the absence of nodal disease (pN0) or certify the highest pN category [118]. How to perform this intraoperative nodal evaluation has been a matter of debate for decades. In 1997, the term systematic nodal dissection was proposed to describe the removal of mediastinal and hilar-pulmonary lymph nodes [120]. The mediastinal part of systematic nodal dissection has two standards: the *en bloc* removal of the fatty tissue and lymph nodes of the ipsilateral mediastinum or the removal of three lymph nodes from three nodal stations, always including the subcarinal nodes. This manoeuvre is followed by the dissection of the hilar and intrapulmonary lymph nodes. An acceptable intraoperative nodal evaluation must include, at least, six lymph nodes, three from the mediastinum, including the subcarinal, and three from the hilar and intrapulmonary nodal stations. This minimum requirement is incorporated in the definition of pN0 proposed by the UICC [121]. The location of the mediastinal lymph nodes to be removed was further defined when the IASLC proposed its definitions of complete resection, for which an adequate nodal evaluation is fundamental. The required evaluation of mediastinal lymph nodes, when an *en bloc* resection is not performed, depends on the lobar location of the primary tumour [122, 123]. For the right upper and middle lobes, the nodal stations to explore are the subcarinal and one of the following: superior and inferior paratracheal nodes and the pretracheal nodes, now included in the right paratracheal, according to the lymph node map proposed by the IASLC [21]. For the right lower lobe, subcarinal and right inferior paratracheal, and either the para-oesophageal or the pulmonary ligament nodes. For the left upper lobe, subcarinal, subaortic and anterior mediastinal nodes. For the left lower lobe, subcarinal, para-oesophageal and pulmonary ligament nodes. This type of evaluation was called lobe-specific systematic nodal dissection, but, strictly speaking, it is a systematic sampling [124]. If this minimal requirement of intraoperative nodal assessment were not met, the IASLC proposed to call the resection uncertain. If macroscopic or microscopic tumour was left in the operative field, the resection would be incomplete, regardless of the nodal evaluation. The definitions proposed by the IASLC have been validated. There are significant differences in survival when complete, uncertain and incomplete resections are compared, which proved their clinical relevance in the staging and treatment of lung cancer [125].

The scenario in 1997 was quite different from the one we are experiencing now, two decades later, when videothoroscopic resections are becoming the standard of care [126]. This change in surgical approach has raised three questions concerning the feasibility of systematic nodal dissection by videothoroscopic approach,

the prognostic impact of systematic nodal dissection and sampling, and their complications. Regarding the feasibility of systematic nodal dissection performed by videothoracoscopy, recent reports show that it can be performed whether videothoracoscopy is performed with three, two or one ports, or with a robot [127–131].

The impact on survival of systematic nodal dissection and sampling still is controversial. A randomised trial comparing sampling and complete mediastinal lymphadenectomy for clinical T1-T2 N0 and non-hilar N1 revealed no differences in 5-year disease-free survival rates or in local, regional and distant recurrence [132]. However, in those patients undergoing complete lymphadenectomy, a median number of 18 nodes (range 1–72 for right-sided tumours and 4–69 for left-sided tumours) were additionally removed after sampling, and 21(4%) patients were found to have occult N2 disease [133]. A report on lobe-specific systematic nodal dissection found that, although there were no statistically significant differences when survival was compared with that of systematic nodal dissection, mediastinal nodal recurrence was significantly higher in the group of patients who underwent lobe-specific systematic nodal dissection [134]. Considering that the number of removed lymph nodes has prognostic impact even in patients with pN0 tumours, and that quantification of nodal disease based on the number of involved nodal zones [135], on the number of involved nodal stations [11] or on the lymph node ratio, that is the number of involved lymph nodes divided by the number of removed lymph nodes [136], also has prognostic implications, complete lymphadenectomy has clear advantages for the individual patient, although these advantages remain occult when series of patients are analysed. In addition, systematic nodal dissection is not associated with higher complication rates when compared to sampling [137, 138]. It is also important to realise that the concept of lobe-specific systematic nodal dissection is based on statistics, on the probability of nodal involvement depending on the lobar location of the tumour, but it is not exact [139–141]. Involved lymph nodes may remain beyond the nodal stations explored, and their presence has a deleterious effect on prognosis [142]. Lobe-specific systematic nodal dissection certainly is better than no nodal dissection at all, but systematic nodal dissection is the only procedure that ensures an accurate staging and the probability of prolonged survival for the individual patient.

Pleural lavage cytology before and after resection is a cheap and rapid method for refining intraoperative staging and postoperative prognosis. It is positive in between 3 and 7% of patients, even in those with stage I adenocarcinoma. A positive pleural lavage is consistently associated with higher rates of recurrence and lower survival in reported series [143–150] and in meta-analyses [151–153]. It has been suggested to increase the T category of those tumours with positive pleural lavage cytology, but it already has a code in the TNM staging system: R1 (cy+). Therefore, it should be considered a microscopic incomplete resection.

Pathological issues in TNM staging

In the eighth edition of the TNM classification of lung cancer there are several important changes involving pathology issues. These include the introduction of concepts of AIS, MIA and LPA, as well as the usefulness of histological comparison of multiple lung adenocarcinomas using the tool of comprehensive histological subtyping [4, 5, 10, 80, 154]. In addition, pathological issues related to determining the extent of tumour invasion of anatomic sites such as the visceral pleura remain the same as in previous staging classifications [155].

Addition of Tis (AIS) for adenocarcinoma in situ and T1mi for minimally invasive adenocarcinoma

It was recommended to add AIS to the category of Tis, which previously consisted only of squamous cell carcinoma *in situ* (SCIS). So now, AIS is coded as Tis (AIS) in distinction from Tis (SCIS) [6, 8, 10]. AIS is defined as a localised small (≤ 3 cm) adenocarcinoma with tumour cells growing along pre-existing alveolar walls in a lepidic pattern where invasion of stroma, vessels, alveolar spaces or visceral pleura are lacking (table 5). In addition, invasive adenocarcinoma patterns such as solid, acinar, papillary or micropapillary patterns are absent. Spread through air spaces (STAS), consisting of tumour cells appearing within air spaces in the lung parenchyma beyond the edge of the main tumour, should be absent. AIS can have either a non-mucinous, mucinous or mixed mucinous and non-mucinous histology, but most cases of AIS are non-mucinous, consisting of type II pneumocytes and/or club (formerly Clara) cells [4, 5]. The diagnosis of both AIS and MIA requires complete histological sampling.

Cases of adenocarcinoma with a pure lepidic pattern larger than 3.0 cm are extremely rare and not well documented in the literature. Therefore, there is insufficient data to know their clinical behaviour and it is recommended to classify such tumours as LPA and to assign a pathological T1a category. If the entire tumour has been processed for histological examination and no invasion is identified, the possibility of AIS can be mentioned in a comment [4, 5].

It was also recommended to classify MIA as T1mi [6, 8, 10]. MIA is defined as a small (≤ 3 cm), solitary adenocarcinoma, with a lepidic predominant pattern and invasion measuring ≤ 5 mm (table 5) [4, 5]. The invasive area should be measured in the largest dimension [4, 5]. In some cases the invasive component

TABLE 5 Pathological criteria for adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma

Adenocarcinoma <i>in situ</i>	Minimally invasive adenocarcinoma
A small tumour ≤3 cm	A small tumour ≤3 cm
A solitary adenocarcinoma [#]	A solitary adenocarcinoma [#]
Pure lepidic growth	Predominantly lepidic growth
No stromal, vascular or pleural invasion	Invasive component ≤0.5 cm in greatest dimension in any one focus
No pattern of invasive adenocarcinoma (such as acinar, papillary, micropapillary, solid, colloid, enteric, fetal or invasive mucinous adenocarcinoma)	Invasive component to be measured includes 1) any histological subtype other than a lepidic pattern (such as acinar, papillary, micropapillary, solid, colloid, fetal or invasive mucinous adenocarcinoma); 2) tumour cells infiltrating myofibroblastic stroma
No STAS	The diagnosis of minimally invasive adenocarcinoma is excluded if the tumour 1) invades lymphatics, blood vessels, air spaces or pleura, 2) contains tumour necrosis, 3) STAS
Cell type mostly non-mucinous (type II pneumocytes or Clara (club) cells), but rarely may be mucinous (tall columnar cells with basal nuclei and abundant cytoplasmic mucin, sometimes resembling goblet cells)	The cell type in most cases consists of non-mucinous (type II pneumocytes or Clara (club) cells), but rarely may be mucinous (tall columnar cells with basal nuclei and abundant cytoplasmic mucin, sometimes resembling goblet cells)
Nuclear atypia is absent or inconspicuous	
Septal widening with sclerosis/elasticity is common, particularly in non-mucinous adenocarcinoma <i>in situ</i>	

Modified from references [4, 5]. STAS: spread through air spaces. #: when multiple AIS are found, they should be regarded as separate primaries rather than intrapulmonary metastases.

represents a single focus that can be measured grossly or in some cases, where the entire tumour fits on a single H&E slide, it can be measured microscopically with a ruler. When invasion consists of multiple foci, or the invasive focus does not fit on a single slide, it can be impossible to measure with a ruler on the microscopic slide. In such cases it is proposed to estimate the invasive size by multiplying the total percentage of invasive components determined by comprehensive histological subtyping by the total tumour size. For example in a 1.5 cm tumour with 20% invasive histological components (acinar, papillary, micropapillary or solid) the invasive size would be estimated at 0.3 cm [10, 156]. Most MIA are non-mucinous but rare cases of mucinous or mixed mucinous and non-mucinous MIA occur [4, 5, 10, 157]. The lepidic component of non-mucinous type of MIA consists of a proliferation of atypical type II pneumocytes and/or club (formerly Clara) cells along the alveolar walls. The mucinous type of MIA consists of columnar cells with abundant apical mucin and small basally oriented nuclei that may show goblet cell features.

In MIA, the invasive component can be identified in the following way: 1) non-lepidic histological subtypes such as acinar, papillary, micropapillary and/or solid or 2) infiltration of myofibroblastic stroma. The diagnosis of MIA is excluded if the tumour 1) invades lymphatics, blood vessels, alveolar spaces or pleura, 2) exhibits tumour necrosis, or 3) shows STAS [4, 5]. In tumours where the invasive component is greater than 0.5 cm, the diagnosis should be lepidic predominant adenocarcinoma. In addition, if the total size is larger than 3.0 cm, the tumour is best classified as lepidic predominant adenocarcinoma and pathological T1a. A recent study suggests that rare cases, otherwise fitting criteria for MIA, that have a total size larger than 3.0 cm may be classified as MIA. In this study the maximum tumour size was 4.7 cm [158]. However, this proposal needs more validation.

Use invasive size for T categories based on size in non-mucinous lung adenocarcinoma with a lepidic pattern

The invasive size is now recommended for the determination of the T category based on tumour size in lung non-mucinous adenocarcinomas with a lepidic component. The lepidic component is excluded from the measurement. The same principles in measurement mentioned in MIA apply for these tumours as well. So, in addition to documenting the total tumour size (*i.e.* the maximum measurement of the ground glass or lepidic component), the invasive component needs to be documented and this is what is used for the size of the T category. This principle does not apply to invasive mucinous adenocarcinomas for which the total tumour size is used to determine the T category [10].

Adenocarcinomas with predominant lepidic growth, if they have an invasive component larger than 0.5 cm, are classified as lepidic predominant adenocarcinoma.

Visceral pleural invasion

Pathological involvement of the visceral pleura by lung cancer is classified at three levels of invasion including into the pleura beyond the main elastic layer (PL1), to the visceral pleural surface (PL2) and into the chest wall (PL3) [155]. When the tumour does not reach the elastic layer, it is classified as PL0 and this feature is not used as a T descriptor; when PL1 or PL2, it is T2; and when PL3, it is T3. Analysis of the IASLC database in preparation for revisions for the eighth edition of the TNM classification confirmed the worse prognosis for PL1 and PL2, but it also showed that PL2 had a significantly worse prognosis compared to PL1 [9]. In cases where the relationship to the pleura is not clear, elastic stains may be very helpful in clarifying whether the tumour invades into the visceral pleura.

Conclusion

Clinical and pathological staging of lung cancer by means of a thoughtful combination of imaging and metabolic techniques, endoscopies, minimally invasive surgical interventions, detailed resection, and systematic pathological examination provide the greatest certainty to indicate initial therapy, assign prognosis before and after treatment, and make further therapeutic decisions after tumour resection. The existing clinical practice guidelines and the innovations in pathological and anatomic classifications of lung cancer, as well as in the imaging procedures, endoscopies and surgical procedures, increase the precision and the thoroughness of the staging process and, thus, assist the clinician in the management of lung cancer patients.

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