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Lung cancer staging: a concise update

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Abstract

Diagnosis and clinical staging of lung cancer are fundamental to plan therapy. The techniques for clinical staging – 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 to achieve a complete resection. In resected tumours, pathologic staging, with the systematic study of the resected specimens, is the strongest prognosticator 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 8th 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.

Keywords: adenocarcinoma *in situ*; computed tomography; endobronchial ultrasonography, lung cancer; lung cancer staging; lymphadenectomy; mediastinoscopy; minimally invasive adenocarcinoma; positron emission tomography

Introduction

The thoracic oncology community worldwide 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 in this decade. [1, 2, 3] Well-researched and profusely documented, these guidelines have set the pace of lung cancer staging in most parts of the world. They emphasize the importance of achieving the highest possible certainty at clinical and pathologic staging by the thoughtful combination of imaging, endoscopies, minimally invasive surgical procedures, and thorough intraoperative staging, as well as by a sound pathologic 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 plan initial therapy, and staging after tumour resection is the strongest prognosticator and provides essential information to make 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 8th 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 (AJCC) and the IASLC. [6, 7, 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, an x-ray of the chest 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 x-ray 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 specially the integrated PET-CT technique have changed the staging of lung cancer, and should be routinely performed for optimal clinical staging. Other techniques, like 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 8th 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 histopathologic 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 subjected to be revised after histopathologic 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 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. 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. [23] 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. demonstrated a sensitivity of 0.70 for CT and of 0.85 for PET-CT. [25] In addition, Prenzel et al. showed that 77% of patients without nodal involvement had nodes > 1cm in short axis, and that 12% of patients with N1 or N2 tumours did not present any node with a short axis > 1cm. [26] PET-CT shows better results than CT alone and PET alone in the diagnostic 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. demonstrated that diffusion-MRI has equal sensitivity than PET-CT (0.75 vs. 0.72, respectively), but higher specificity (PET-CT 0.89 vs. MRI 0.95). [31] 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 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 8th edition of the TNM classification provides recommendations on how to differentiate separate tumour nodules from multifocal adenocarcinomas at clinical and pathologic 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 unrecognized 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] Deusch et al. 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. [44] 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, 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. [48] 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 18F-fluorothymide, 11C-methionine, 18F-fluoromisonidazole, and 68Ga-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, 68Ga-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, 18F-NaF PET showed no false

negatives in the detection of bone metastases, while bone scan and SPECT had 6 and 1 false negatives, respectively. [53] Also, 18F-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 pathologic 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 randomized controlled trial, a conventional TBNA performed during a first standard bronchoscopy can be a valuable mediastinal staging tool in clearly enlarged (defined as >15mm 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 pathologic 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 visualize 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 3. [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 NSCLC

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 multicenter 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 NSCLC 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 NSCLC, a post-test probability of greater then 10% is expected requiring another invasive staging text, 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 NSCLC

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 randomized controlled trial (RCT). [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 RCT 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 is no RCT 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 (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 to patients and cost-effective compared to using two scopes by two endoscopists, reducing the need for surgical staging procedures. [74-77]

Imaging guided (US/CT) transthoracic techniques

Transthoracic needle aspiration (TTNA) and transthoracic needle core biopsy (TNCB)

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, 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 transthoracic needle core biopsies is that they result in a higher yield of tissue speciemns for mutation analysis. [79] Complication rate of both techniques is low, being the pneumothorax the most frequent (7-10%). [1, 79, 80]

Thoracocentesis

Patients with suspected lung cancer presenting with pleural effusion should undergo thoracocentesis with cyto-pathologic 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)

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 localize at VATS. Several techniques have been developed to facilitate their intraoperative detection. [85] Applying these targeting methods, the success rate to identify nodules at 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]

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%, being arrhythmias 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

(≤3cm) 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 visualization 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%, being the temporal left recurrent laryngeal nerve palsy the most frequent [1, 101-106].

Anterior mediastinotomy (the classic Chamberlain procedure) consists on 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 NPV 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 NPV of 0.91 have been described (Table 3). Complication rate ranges from 0 to 7.2%, although the majority of them are not specific of 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 pathologic 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 were recently developed: videoassisted 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 > 3cm. Regarding complications, published series describe a 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 video-assisted thoracoscopic surgery, 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 pathologic (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 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 were 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 videothoracoscopic 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 videothoracoscopic 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 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 to 72 for right-sided tumours and 4 to 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 realize 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 quick way to refine 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.

Pathologic issues in TNM staging

In the 8th edition of the TNM classification of lung cancer there are several important changes involving pathology issues. These include the introduction of concepts of adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA) and lepidic predominant adenocarcinoma (LPA) as well as the usefulness of histologic comparison of multiple lung adenocarcinomas using the tool of comprehensive histologic subtyping. [4, 5, 10, 80, 154] In addition, pathologic 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 localized 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 histologic 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 pathologic T1a category. If the entire tumour has been processed for histologic 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 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 histologic subtyping times the total tumour size. For example in a 1.5 cm tumour with a 20% of invasive histologic 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 spread through air spaces. [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 pathologic 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. [157] 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

Pathologic 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 8th 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 pathologic staging of lung cancer by means of a thoughtful combination of imaging and metabolic techniques, endoscopies, minimally invasive surgical interventions, detailed resection, and systematic pathologic examination provide the

highest 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 pathologic 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.

References

1 Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: e211S-e250S.

2 De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2014;45:787-98.

3 Lardinois D, De Leyn P, Van Schil P et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg* 2006;30:787-792.

4 Travis WD, Brambilla E, Noguchi M, et al. The New IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. *J Thorac Oncol* 2011;6:244-285.

5 Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: International Agency for Research on Cancer; 2015.

6 Brierley JD, Gospodarowicz MK, Wittekind Ch, eds. *UICC TNM Classification of Malignant Tumours*. Eighth edition. Oxford: Wiley Blackwell; 2017.

7 Amin MB, ed. *AJCC Cancer Staging Manual*. Eighth edition. Springer; 2017.

8 Rami-Porta R, ed. *IASLC Staging Manual in Thoracic Oncology*. North Fort Myers, FL: Editorial Rx Press; 2016.

9 Rami-Porta R, Bolejack V, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015;10:990-1003.

10 Travis WD, Asamura H, Bankier A et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2016;11:1204-1223.

11 Asamura H, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015;10:1675-1684.

12 Eberhardt WEE, Mitchell A, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the M descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015;10:1515-1522.
13 Goldstraw P, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2016;11:39-51.
14 Kirsch J, Ramirez J, Mohammed TL, et al. ACR Appropriateness Criteria: acute respiratory illness in immunocompetent patients. *J Thorac Imaging* 2011;26:W42-4.
15 de Castro J, Cobo M, Isla D, et al. Recommendations for radiological diagnosis and assessment of treatment response in lung cancer: a national consensus statement by the Spanish Society of Medical Radiology and the Spanish Society of Medical Oncology. *Clin Transl Oncol* 2015;17:11-23.
16 Kitajima K, Doi H, Kanda T, et al. Present and future roles of FDG-PET/CT imaging in the management of lung cancer. *Jpn J Radiol* 2016;34:387-399.
17 Hattori A, Matsunaga T, Takamochi K, Shiaki O, Suzuki K. Importance of ground glass opacity component in clinical stage IA radiologic invasive lung cancer. *Ann Thorac Surg* 2017;104:313-320.
18 Kajiwara N, Akata S, Uchida O, et al. Cine MRI enables better therapeutic planning than CT in cases of possible lung cancer chest wall invasion. *Lung Cancer* 2010;69:203-208.
19 Bandi V, Lunn W, Ernst A, Eberhardt R, Hoffmann H, Herth FJ. Ultrasound vs. CT in detecting chest wall invasion by tumor: a prospective study. *Chest* 2008;133:881-886.
20 Bruzzi JF, Komaki R, Walsh GL, et al. Imaging of non-small cell lung cancer of the superior sulcus: part 2: initial staging and assessment of resectability and therapeutic response. *Radiographics* 2008;28:561-572.
21 Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568-577.
22 El-Sherief AH, Lau CT, Wu CC, Drake RL, Abbott GF, Rice TW. International association for the study of lung cancer (IASLC) lymph node map: radiologic review with CT illustration. *Radiographics* 2014;34:1680-1691.

23 El-Sherief AH, Lau CT, Obuchowski NA, Mehta AC, Rice TW, Blackstone EH. Cross-disciplinary analysis of lymph node classification in lung cancer on computed tomography. *Chest* 2017;151:776-785.

24 Gelberg J, Grondin S, Tremblay A. Mediastinal staging for lung cancer. *Can Respir J* 2014;21:159-161.

25 Shim SS, Lee KS, Kim BT, et al. Non-small cell lung cancer: prospective comparison of integrated FDG PET-CT and CT alone for preoperative staging. Radiology. 2005;236:1011-1019.

26 Prenzel KL, Mönig SP, Sinning JM, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. Chest. 2003;123:463-467.

27 Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med* 2003;139:879-892.

28 Zhao L, He ZY, Zhong XN, Cui ML. 18FDG-PET/CT for detection of mediastinal nodal metastasis in non-small cell lung cancer: a meta-analysis. *Surg Oncol* 2012;21:230-236.

29 Lv YL, Yuan DM, Wang K, et al. Diagnostic performance of integrated positron emission tomography/computed tomography for mediastinal lymph node staging in non-small cell lung cancer: a bivariate systematic review and meta-analysis. *J Thorac Oncol* 2011;6:1350-1358.

30 Malayeri AA, el Khouli RH, Zaheer A, et al. Principles and applications of diffusion-weighted imaging in cancer detection, staging, and treatment follow-up. *Radiographics* 2011;31:1773-1791.

31 Wu LM, Xu JR, Gu HY, et al. Preoperative mediastinal and hilar nodal staging with diffusion-weighted magnetic resonance imaging and fluorodeoxyglucose positron emission tomography/computed tomography in patients with non-small-cell lung cancer: which is better? *J Surg Res* 2012;178:304-314.

32 Pauls S, Schmidt SA, Juchems MS, et al. Diffusion-weighted MR imaging in comparison to integrated [(1)(8)F]-FDG PET/CT for N-staging in patients with lung cancer. *Eur J Radiol* 2012;81:178-182.

33 Sommer G, Wiese M, Winter L, et al. Preoperative staging of non-small-cell lung cancer: comparison of whole-body diffusion-weighted magnetic resonance imaging and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography. *Eur Radiol* 2012;22:2859-2867.

34 Shen G, Lan Y, Zhang K, Jia Z. Comparison of 18F-FDG PET/CT and DWI for detection of mediastinal nodal metastasis on non-small cell lung cancer: A meta-analysis. *PLoS One* 2017;2;12:e0173104.

35 Detterbeck FC, Marom EM, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the application of TNM staging rules to lung cancer presenting as multiple nodules with ground glass or lepidic features or a pneumonic type of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol* 2016;11:666-680.

36 Detterbeck FC, Bolejack V, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the classification of lung cancer with separate tumor nodules in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016;11:681-692.

37 Harders SW, Balyanikowa S, Fischer BM. Functional imaging in lung cancer. *Clin Physiol Funct Imaging* 2014;34:340-355.

38 Metser U, Miller E, Lerman H, Lievshitz G, Avital S, Even-Sapir E. 18F-FDG PET/CT in the evaluation of adrenal masses. *J Nucl Med* 2006;47:32-37.

39 Ozcan Kara P, Kara T, Kara Gedik G, et al. The role of fluorodeoxyglucose-positron emission tomography/computed tomography in differentiating between benign and malignant adrenal lesions. *Nucl Med Commun* 2011;32:106-112.

40 Boland GW, Dwamena BA, Jagtiani Sangwaiya M et al . Characterization of adrenal masses by using FDG PET: a systematic review and meta-analysis of diagnostic test performance. Radiology. 2011 Apr;259(1):117-126

41 O'Dowd EL, Kumaran M, Anwar S, Palomo B, Baldwin DR. Brain metastases following radical surgical treatment of non-small cell lung cancer: is preoperative brain imaging important? *Lung Cancer* 2014;86:185-9.

42 Detterbeck FC, Postmus PE, Tanoue LT. The stage classification of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e191S-e210S.

43 Millon D, Byl D, Collard P, et al. Could new reconstruction CT techniques challenge MRI for the detection of brain metastases in the context of initial lung cancer staging? Eur Radiol 2017. doi: 10.1007/s00330-017-5021-7. [Epub ahead of print].

44 Deushcl C, Nensa F, Grueneisen J, et al. Diagnostic impact of integrated 18F-FDG PET/MRI in cerebral staging of patients with non-small cell lung cancer. *Acta Radiol* 2017; 58:991-996.

45 Cho H, Lee HY, Kim J, et al. Pure ground glass nodular adenocarcinomas: Are preoperative positron emission tomography/computed tomography and brain magnetic resonance imaging useful or necessary? *J Thorac Cardiovasc Surg* 2015;150:514-520.

46 Mitchell MD, Aggarwal C, Tsou AY, Torigian DA, Treadwell JR. Imaging for the pretreatment staging of small cell lung cancer: A systematic review. *Acad Radiol* 2016;23:1047-1056.

47 Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. *Ann Oncol* 2007;18:338-345.

48 Usuda K, Sagawa M, Maeda S, et al. Diagnostic performance of whole-body Diffusion-weighted imaging compared to PET-TC plus brain-MRI in staging clinically resectable lung cancer. *Asian Pac J Cancer Prev* 2016;17:2775-2780.

49 Schaarschmidt BM, Grueneisen J, Metzenmacher M, et al. Thoracic staging with ^{18}F-FDG PET/MR in non-small cell lung cancer – does it change therapeutic decisions i comparison to ^{18}F-FDG PET/CT? *Eur Radiol* 2017;27:681-688.

50 Lee SM, Goo JM, Park CM, et al. Preoperative staging of non-small cell lung cancer: prospective comparison of PET/MR and PET/CT. *Eur Radiol* 2016;26:3850-3857.

51 Yi CA, Lee KS, Lee HY et al. Coregistered whole body magnetic resonance imaging-positron emission tomography (MRI-PET) versus PET-computed tomography plus brain MRI in staging resectable lung cancer. Comparison of clinical effectiveness in a randomized trial. Cancer 2013;119:1784-1791.

52 Szyszko TA, Yip C, Szlosarek P, Goh V, Cook GJR. The role of new PET tracers for lung cancer. *Lung Cancer* 2016;94:7-14.

53 Schirrmeister H, Glatting G, Hetzel J, et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18F)-labeled NaF PET in newly diagnosed lung cancer. *J Nucl Med.* 2011;42:1800–1804.

54 Holty J, Kuschner W, Gould M. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. *Thorax* 2005;60:949-955.

55 Fiorelli A, Santoriello C, Di Natale D, et al. In the era of ultrasound technology, could conventional transbronchial needle aspiration still play a role in lung cancer mediastinal staging? *J Thorac Dis* 2017;9(Suppl5):S386-394.

56 Bonifazi M, Tramacere I, Zuccatosta L, et al. Conventional versus Ultrasound-Guided Transbronchial Needle Aspiration for the Diagnosis of Hilar/Mediastinal Lymph Adenopathies: A Randomized Controlled Trial. Respiration. 2017;94:216-223.

57 Lee HS, Lee GK, Lee HS, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? *Chest* 2008;134:368-374.

58 Yasufuku K, Pierre A, Darling G, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg* 2011;142:1393-1400.

59 Hwangbo B, Lee GK, Lee HS,et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. *Chest* 2010;138:795–802.

60 Oki M, Saka H, Ando M, et al. Endoscopic ultrasound-guided fine needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration: are two better than one in mediastinal staging of non-small cell lung cancer? *J Thorac Cardiovasc Surg* 2014;148:1169-1177.

61 von Bartheld MB, van Breda A, Annema JT. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. *Respiration* 2014;87:343-351.

62 Yarmus L, Akulian J, Gilbert C, et al. Comparison of moderate versus deep sedation for endobronchial ultrasound transbronchial needle aspiration. *Ann Am Thorac Soc* 2013;10:121-126.

63 Shingyoji M, Nakajima T, Yoshino M, et al. Endobronchial ultrasonography for positron emission tomography and computed tomography-negative lymph node staging in non-small cell lung cancer. *Ann Thorac Surg* 2014;98:1762-1767.

64 Ong P, Grosu H, Eapen GA, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for systematic nodal staging of lung cancer in patients with N0 disease by computed tomography and integrated positron emission tomography-computed tomography. *Ann Am Thorac Soc* 2015;12:415-419.

65 Vial M, O'Connell O, Grosu H, et al. Diagnostic performance of endobronchial ultrasound-guided mediastinal lymph node sampling in early stage non-small cell lung cancer: A prospective study. *Respirology* 2018;23:76-81.

66 Naur T, Konge L, Clementsen P. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of patients with non-small cell lung cancer without mediastinal nodal involvement at positron emission tomography-computed tomography. *Respiration* 2017;94:279-284.

67 Dooms C, Tournoy KG, Schuurbiers O, et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. *Chest* 2015;147:209-2015.

68 Decaluwé H, Dooms C, D'Journo XB, et al. Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: a prospective multicentre study. *Eur Respir J* 2017;50: 1701493 [https://doi.org/10.1183/13993003.01493-2017]

69 Yasufuku K, Nakajima T, Waddell T, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for differentiating N0 versus N1 lung cancer. *Ann Thorac Surg* 2013;96:1756-1760.

70 De Leyn P, Lardinois D, Van Schil PE, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg* 2007;32:1-8.

71 Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010;304:2245-2252.

72 Tournoy K, Keller S, Annema J. Mediastinal staging of lung cancer: novel concepts. *Lancet Oncol* 2012;13:e221-229.

73 Um S, Kim H, Jung S, et al. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small cell lung cancer. *J Thorac Oncol* 2015;10:331-337.

74 Korevaar D, Crombag L, Cohen J, et al. Added value of combined endobronchial and oesophageal endosconography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis. *Lancet Respir Med* 2016;4:960-968.

75 Lardinois D, Schallberger A, Betticher D, et al. Postinduction video-mediastinoscopy is as accurate and safe as video-mediastinoscopy in patients without pretreatment for potentially operable non-small cell lung cancer. *Ann Thorac Surg* 2003;75:1102-1106.

76 Kang H, Hwangbo B, Lee GK, et al. EBUS-centered versus EUS-centered mediastinal staging in lung cancer: a randomised controlled trial. *Thorax* 2014;69:261-268.

77 Oki M, Saka H, Ando M, et al. Transbronchial versus transesophageal needle aspiration using an ultrasound bronchoscope for the diagnosis of mediastinal lesions: a randomised study. *Chest* 2015;147:1259-1266.

78 Yang W, Jiang H, Khan AN, et al. Transthoracic needle aspiration in solitary pulmonary nodule. *Transl Lung Cancer Res* 2017; 6:76-85.

79 Rivera MP, Mehta AC. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: ACCP evidence-based clinical practice guidelines. *Chest* 2013; 143:e142S-e165S.

80 De Margerie-Mellon C, de Bazelaire C, Amorim S, et al. Diagnostic yield and safety of computed tomography-guided mediastinal core needle biopsies. *J Thorac Imaging* 2015; 30:319-327.

81 Zarogoulidis C, Zarogoulidis P, Darwiche K, et al. Malignant pleural effusion and algorithm management. *J Thorac Dis* 2013; 5: S413-S419.

82 Assawasaksakul T, Boonsarngsuk V, Incharoen P. A comparative study of conventional cytology and cell block method in the diagnosis of pleural effusion. *J Thorac Dis* 2017; 9:3161-3167.

83 Wang XJ, Yang Y, Wang Z, et al. Efficacy and safety of diagnostic thoracoscopy in undiagnosed pleural effusions. *Respiration* 2015; 90:251-5.

84 Detterbeck FC, Nicholson AG, Franklin WA, et al. The IASLC Lung Cancer Staging Project: Summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eight edition of the TNM classification. *J Thorac Oncol* 2016;11:639-650.

85 Lin MW, Chen JS. Image-guided techniques for localizing pulmonary nodules in thoracoscopic surgery. *J Thorac Dis* 2016;8:S749-S755.

86 Park CH, Han K, Hur J, et al. Comparative effectiveness and safety of preoperative lung localization of pulmonary nodules: a systematic review and meta-analysis. *Chest* 2017; 151: 316-328.

87 Celik M, Halezeroglu S, Senol C, et al. Video-assisted thoracoscopic surgery: experience with 341 cases. *Eur J Cardiotrhorac Surg* 1998; 14: 113-116.

88 Krasna MJ. The role of thoracoscopy in the management of cancer patients. *Semin Oncol* 2008; 35: 129-133.

89 Mizukami Y, Ueda N, Adachi H, et al. Long-term outcomes after video-assisted thoracoscopic pericardiectomy for pericardial effusion. *Ann Thorac Cardiovasc Surg* 2017. Doi: 10.5761/atcs.oa.17-00046.

90 Cerfolio RJ, Bryant AS, Eloubeidi MA. Accessing the aortopulmonary window (#5) and the paraaortic (#6) lymph nodes in patients with non-small cell lung cancer. *Ann Thorac Surg* 2007; 84:940-945.

91 Massone PP, Lequaglie C, Magnani B, et al. The real impact and usefulness of video-assisted thoracoscopic surgery in the diagnostic and therapy of clinical lymphadenopathies of the mediastinum. *Ann Surg Oncol* 2003;10:1197-1202.

92 Sebastián-Quetglás F, Molins L, Baldó X, et al. Clinical value of video-assisted thoracoscopy for preoperative staging of non-small cell lung cancer. A prospective study of 105 patients. *Lung Cancer* 2003;42:297-301.

93 Loscertales J, Jimenez-Merchan R, Congregado M, et al. Video-assisted surgery for lung cancer. State of the art and personal experience. *Asian Cardiovasc Thorac Ann* 2009;17:313-326.

94 Porte HL, Janecki-Delebecq TJ, Finzi L, et al. Pericardioscopy for primary management of pericardial effusion in cancer patients. *Eur J Cardiothorac Surg* 1999; 16:287-291.

95 Little AG, Ferguson MK. Pericardioscopy as adjunct to pericardial window. *Chest* 1986; 89:53-55.

96 Maisch B, Ristic A, Pankuweit S. Evaluation and management of pericardial effusion in patients with neoplastic disease. *Prog Cardiovasc Dis* 2010; 53:157-63.

97 Kondos GT, Rich S, Levitsky S. Flexible fiberoptic pericardioscopy for the diagnosis of pericardial disease. *J Am Coll Cardiol* 1986; 7:432-434.

98 Saab J, Hoda RS, Narula N, et al. Diagnostic yield of cytopathology in evaluating pericardial effusions: Clinicopathologic analysis of 419 specimens. *Cancer Cytopathol* 2017; 125:128-137.

99 Wurtz A, Chambon JP, Millaire A, Saudemont A, Ducloux G. Pericardioscopy: techniques, indications and results. Apropos of an experience with 70 cases. *Ann Chir* 1992;46:188-193.

100 Adebibe M, Jarral OA, Shipolini AR, et al. Does video-assisted mediastinoscopy have a better lymph node yield and safety profile than conventional mediastinoscopy? *Interact Cardiovasc Thorac Surg* 2012; 14:316-319.

101 Wei B, Bryant AS, Minnich DJ, et al. The safety and efficacy of mediastinoscopy when performed by general thoracic surgeons. *Ann Thorac Surg* 2014; 97:1878-1883.

102Sayar A, Citak N, Metin M, et al. Comparison of video-assisted mediastinoscopy and video-assisted mediastinoscopic lymphadenectomy for lung cancer. *Gen Thorac Cardiovasc Surg* 2011; 59:793-798.

103Anraku M, Miyata R, Compeau C, et al. Video-assisted mediastinoscopy compared with conventional mediastinoscopy: are we doing better? *Ann Thorac Surg* 2010; 89:1577-1581.

104Leschber G, Sperling D, Klemm W, et al. Does video-mediastinoscopy improve the results of conventional mediastinoscopy? *Eur J Cardiothorac Surg* 2008;33:289-293.

105Kimura H, Yasufuku K, Ando S, et al. Indications for mediastinoscopy and comparison of lymph node dissections in candidates for lung cancer surgery. *Lung Cancer* 2007;56:349-355.Venissac N, Alifano M, Mouroux J. Video-assisted mediastinoscopy: experience from 240 consecutive cases. *Ann Thorac Surg* 2003;76:208-212.

106Witte B, Wolf M, Hillebrand H, et al. Extended cervical mediastinoscopy revisited. *Eur J Cardiothorac Surg* 2014;45:114-119.

107Obiols C, Call S, Rami-Porta R, et al. Extended cervical mediastinoscopy: mature results of a clinical protocol for staging bronchogenic carcinoma of the left lung. *Eur J Cardiothorac Surg* 2012;41:1043-1046.

108Metin C, Citak N, Sayar A, et al. The role of extended cervical mediastinoscopy in staging of non-small cell lung cancer of the left lung and a comparison with integrated positron emission tomography and computed tomography: does integrated positron emission tomography and computed tomography reduce the need for invasive procedures? *J Thorac Oncol* 2011;6:1713-1719.

109Freixinet Gilart J, García PG, de Castro FR, et al. Extended cervical mediastinoscopy in the staging of bronchogenic carcinoma. *Ann Thorac Surg* 2000;70:1641-1643.

110Ginsberg RJ, Rice TW, Golberg M, et al. Extended cervical mediastinocopy. A single staging procedure for bronchogenic carcinoma of the left upper lobe. *J Thorac Cardiovasc Surg* 1987;94:673-678.

111Dawson AG, Waller DA. Cervical mediastino-thoracoscopy. In: Zielinski M, Rami-Porta R, eds, *The transcervical approach in thoracic surgery*. Heidelberg, Springer, 2014; pp. 45-51.

112Call S, Obiols C, Rami-Porta R, et al. Video-assisted mediastinoscopic lymphadenectomy for staging non-small cell lung caner. *Ann Thorac Surg* 2016;1326-1333.

113Turna A, Demirkaya A, Ozkul S, et al. Video-assisted mediastinocopic lymphadenectomy is associated with better survival than mediastinoscopy in patients with resected non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2013; 146:774-780.

114Witte B, Wolf R, Hürtgen M, et al. Video-assisted mediastinoscopic surgery: clinical feasibility and accuracy of mediastinal lymph node staging. *Ann Thorac Surg* 2006; 82:1821-1827.

115Zielinski M. Transcervical extended mediastinal lymphadenectomy (TEMLA): the standard procedure and its variations. In: Zielinski M, Rami-Porta R, eds. *The transcervical approach in thoracic surgery*. Heidelberg, Springer, 2014; pp. 101-116.

116Zielinski M, Hauer L, Hauer J, et al. Transcervical Extended Mediastinal Lymphadenectomy (TEMLA) for staging non-small-cell lung cancer (NSCLC). *Pneumonol Alergol Pol* 2011; 79:196-206.

117Explanatory notes - Specific anatonical sites. In: Wittekind Ch, Compton CC, Brierley J, Sobin LH, eds. *UICC TNM Supplement on Uniform Use*. Fourth edition, Oxford, Wiley-Blackwell, 2012; p: 70.

118Martini N, Ginsberg RJ. Surgical management. In: Pearson FG, Deslauriers J, Ginsberg RJ, Hiebert CA, McKneally MF, Urshel Jr HC, eds. *Thoracic surgery*. New York: Churchill Livingstone; 1995. p. 690-705.

119Goldstraw P. Report on the International workshop on intrathoracic staging, London, October 1996. *Lung Cancer* 1997;18:107-11.

120Site-specific requirements of pT and pN. In: Wittekind Ch, Compton CC, Brierley J, Sobin LH, eds. *UICC TNM Supplement on Uniform Use*. Fourth edition, Oxford, Wiley-Blackwell, 2012; p: 149-150.

121Naruke T, Tsuchiya R, Kondo H, Nakayama H, Asamura H. Lymph node sampling in lung cancer: how should itbe done? *Eur J Cardiothorac Surg* 1999;16(Suppl. 1):17-24.

122Ichinose Y, Kato H, Koike T et al. Completely resected stage IIIA non-small cell lung cancer: the significance of primary tumor location and N2 station. *J Thorac Cardiovasc Surg* 2001;122:803-808.

123Rami-Porta R, Wittekind Ch, Goldstraw P, for the International Association for the Study of Lung Cancer (IASLC) Staging Committee. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer* 2005;49:25-33.

124Gagliasso M, Magliaretti G, Ardissone F. Assessing the prognostic impact of the International Association for the Study of Lung Cancer proposed definitions of complete, uncertain, and incomplete resection in non-small cell lung cancer surgery. *Lung Cancer* 2017;111:124-130.

125Treasure T. Videothoracoscopic resection for lung cancer: moving towards a 'standard of care'. *J Thorac Dis* 2016; 8: E772-E774.

126Liu C-C, Shih C-H, Pennarun N, Cheng C-T. Transition from a multiport technique to a single-port technique for lung cancer surgery: is lymph node dissection inferior using the single-port technique? *Eur J Cardiothorac Surg* 2016;49:i64-i72.

127Yang R, Jiao W, Zhao Y, Qiu T, Wang Y, Luo Y. Lymph node evaluation in totally thoracoscopic lobectomy with two-port for clinical early-stage nonsmall-cell lung cancer: single-center experience of 1086 cases. *Indian J Cancer* 2015; 52 (special issue 2):e134-e139.

128Liu C, Pu Q, Guo C et al. Non-grasping en bloc mediastinal lymph node dissection for video-assisted thoracoscopic lung cancer surgery. *BMC Surgery* 2015; 15: 38. DOI 10.1186/s12893-015-0025-1

129Wang G-S, Wang Z, Wang J, Rao Z-P. Uniportal video-assisted thoracoscopic lobectomy with systematic lymphadenectomy. *J Thorac Dis* 2014;6:1011-1016.

130Toker A, Özyurtkan MO, Demirhan Ö, Ayalp K, Kaba E, Uyumaz E. Lymph node dissection in surgery for lung cancer: comparison of open vs. video-assisted vs. robotic-assisted approaches. *Ann Thorac Cardiovasc Surg* 2016;22:284-290.

131Darling GE, Allen MS, Decker PA et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patients with N0 or N1 (less than hilar) non-small cell carcinoma: Results of the American College of Surgery Oncology Group Z0030 trial. *J Thorac Cardiovasc Surg* 2011;141:662-670.

132Darling GE, Allen MS, Decker PA et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy. Results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. *Chest* 2011; 130: 1124-1129.

133Maniwa T, Okumura T, Isaka M, Nakagawa K, Ohde Y, Kondo H. Recurrence of mediastinal node cancer after lobe-specific systematic nodal dissection for non-small cell lung cancer. *Eur J Cardiothorac Surg* 2013; 44: e59-e64.

134Rusch VW, Crowley J, Giroux DJ, et al. The IASLC lung cancer staging project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classifications for lung cancer. *J Thorac Oncol* 2007;2:603-612.

135Tamura M, Matsumoto I, Saito D, Yoshida S, Takata M, Takemura H. Lymph node ratio as a prognostic factor in patients with pathological N2 non-small cell lung cancer. *World J Surg Oncol* 2016; 14: 295. DOI 10.1186/s1257-016-1048-5

136Allen MS, Darling GE, Pechet TT et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006;81:1013-1019.

137Huang X, Wang J, Chen Q, Jiang J. Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: a systematic review and meta-analysis. *PLoS ONE* 2014; 9: e109979. Doi:10.1371/journal.pone.0109979

138Riquet M, Rivera C, Pricopi C et al. Is the lymphatic drainage of lung cancer lobe-specific? A surgical appraisal. *Eur J Cardiothorac Surg* 2015;47:543-549.

139Riquet M, Pricopi C, Arame A, Le Pimpec Barthes F. From anatomy to lung cancer: questioning lobe-specific mediastinal lymphadenectomy reliability. *J Thorac Dis* 2016;8:2387-2390.

140Riquet M, Pricopi C, Legras A, Arame A, Badia A, Le Pimpec Barthes F. Can mathematics replace anatomy to establish recommnedations in lung cancer surgery? *J Thorac* Dis 2017;9:E327-E332.

141Sun Y, Gao W, Zheng H, Jiang G, Chen C, Zhang L. Mediastinal lymph-nodes metastasis beyond the lobe-specific. An independent risk factors towards worse prognoses. *Ann Thorac Cardiovasc Surg* 2014;20:284-291.

142Aokage K, Yoshida J, Ishii G et al. The impact on survival of positive intraoperative pleural lavage cytology in patients with non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 2010;139:1246-1252.

143Kaneda M, Yokoi K, Ito S et al. The value of pleural lavage cytology examined during surgery for primary lung cancer. *Eur J Cardiothorac Surg* 2012;41:1335-1341.

144Kameyama K, Okumura N, Miyaoka E et al. Prognostic value of intraoperative pleural lavage cytology for non-small cell lung cancer: The influence of positive pleural lavage cytology results on T classification. *J Thorac Cardiovasc Su*rg 2014;148:2659-2664.

145Yanagawa N, Shiono S, Abiko M et al. Positive intraoperative pleural lavage cytology is a predictive marker of disease recurrence in stage I lung adenocarcinoma. *Interact Cardiovasc Thorac Surg* 2014;18:621-625.

146Nakao M, Hoshi R, Ishikawa Y et al. Prognosis of non-small-cell lung cancer patients with positive pleural lavage cytology. *Interact Cardiovasc Thorac Surg* 2015;20:777-782.

147Hokka D, Uchino K, Tane K et al. Pleural lavage cytology as an independent prognostic factor in non-small-cell lung cancer patients with stage I disease and adenocarcinoma. *Mol Clin Oncol* 2015;3:244-248.

148Shimoji M, Nishino M, Sesumi Y et al. Prognostic impact of pleural lavage cytology in patients with primary lung cancer. *Lung Cancer* 2016;102:60-64.

149Shoji F, Yamazaki K, Kouso H, Mori R, Takeo S. The impact of pleural lavage cytology both before and after lung resection on recurrence of non-small cell lung cancer. *Ann Thorac Surg* 2016;101:2141-2146.

150International Pleural Lavage Cytology Collaboratiors. Impact of positive pleural lavage cytology on survival in patients having lung resection for non-small cell lung cancer: An international individual patient data meta-analysis. *J Thorac Cardiovasc Surg* 2010;139:1441-1446.

151Saso S, Rao C, Ashrafian H, Ghaem-Maghami S, Darzi A, Athanasiou T. Positive pre-resection pleural lavage cytology is associated with increased risk of lung cancer recurrence in patients undergoing surgical resection: a meta-analysis of 4450 patients. *Thorax* 2012;67:526-532.

152Wang C-M, Ling Z-G, Wu Y-B et al. Prognostic value of pleural lavage cytology in patients with lung cancer resection: An updated meta-analysis. *PLoS ONE* 2016;11(7):e0157518. Doi:10.1371/journal.pone.0157518.

153Girard N, Deshpande C, Lau C, et al. Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases. *Am J Surg Pathol* 2009;33:1752-1764.

154Travis WD, Brambilla E, Rami-Porta R, et al. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposal for the 7th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2008;3:1384-1390.

155Kadota K, Villena-Vargas J, Yoshizawa A, et al. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous

lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. *Am J Surg Pathol* 2014;38:448-460.

156Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. *Modern Path* 2011;24:653-664.

157Suzuki S, Sakurai H, Masai K, et al. A proposal for definition of minimally invasive adenocarcinoma of the lung regardless of tumor size. *Ann Thorac Surg* 2017;104:1027-1032.

Tables

Table 1. Main innovations in the 8th edition of the tumour, node and metastasis classification of lung cancer

Parameter	Innovation
T descriptors	
Adenocarcinoma *in situ*	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 pathologic 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.

Table 2. Stage grouping of the 8th 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

*Reprinted and adapted with permission from Goldstraw P, Chansky K, Crowley J et al. The IASLC lung cancer staging project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. J Thorac Oncol 2016; 11: 39-51. [13]

Table 3. Accuracy of VATS, VAM and ECM for surgical staging the mediastinum in patients with lung cancer.

VATS								
Author	**Year**	**N**	**P (%)**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LN reached**
Cerfolio [90]	2007	39	92	1	1	1	1	Left side: 5,6,7,8L,9L Right side: 4R, 7, 8L,9L
Massone [91]	2003	55	55	1	1	1	1	
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	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	

Abbreviations: N, number of patients; P: prevalence; PPV: positive predictive value; NPV: negative predictive value; LN reached: lymph node reached; NA: not available; VATS: video-assisted thoracic surgery; VAM: videomediastinoscopy; ECM: extended cervical mediastinoscopy.
*The author report 997 conventional mediastinoscopies and 243 VAM. Staging values were calculated based on the total number. ** Study in the context of clinical N1 dusease.

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

VAMLA								
Author	**Year**	**N**	**P (%)**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LN reached**
Call [113]	2016	151	18	0.96	1	1	0.99	2R, 2L, 4R, 4L,7, 8R, 8L
Turna [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

Abbreviations: N, number of patients; P: prevalence; PPV: positive predictive value; NPV: negative predictive value; LN reached: lymph node reached; VAMLA: videoassisted mediastinoscopic lymphadenectomy; TEMLA: transcervical extended mediastinal lymphadenectomy.

Table 5. Pathologic criteria for adenocarcinoma *in situ* and minimally adenocarcinoma†

Adenocarcinoma *in situ*	**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, foetal or invasive mucinous adenocarcinoma)	Invasive component to be measured includes 1) any histologic subtype other than a lepidic pattern (such as acinar, papillary, micropapillary, solid, colloid, foetal or invasive mucinous adenocarcinoma) 2) tumour cells infiltrating myofibroblastic stroma
No spread through air spaces (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) spread through air spaces (STAS)
Cell type mostly non-mucinous (type II pneumocytes or Clara cells), 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 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/elastosis is common, particularly in non-mucinous	

adenocarcinoma *in situ*	

†Modified from references [4, 5]
‡When multiple AIS are found, they should be regarded as separate primaries rather than intrapulmonary metastases