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Introduction

Staging is one of the most important components in the management of lung cancer. Accurate staging is important because it allows the clinician to predict prognosis and assign appropriate therapy and also provides a system that allows clinicians and researchers to stratify patients into reasonably homogenous groups so that treatment outcomes can be appropriately compared. Tumor staging is broadly broken down into clinical staging and pathologic staging. Clinical stage refers to the best prediction of lung cancer stage prior to the commencement of therapy. Pathologic stage refers to the best prediction of stage following pathologic analysis of the patient's tumor, lymph nodes, and/or metastases and is usually applied following surgical resection or exploration. The distinction between clinical and pathologic stage becomes slightly less clear, however, when patients undergo some form of histologic staging without surgical resection or exploration. Thus, a patient may undergo histologic assessment of mediastinal nodes by endobronchial ultrasound (EBUS) fine-needle aspiration (FNA) prior to surgical resection. The information thus gained is considered to contribute to the clinical not pathologic stage, which would be determined by the pathologic findings at surgery. If the same patient was found to have ipsilateral lymph node metastases at EBUS and then went on to receive nonsurgical therapy, he would be considered to have pathologic stage N2 (p-stage IIIa) disease. Ultimately, pathologic stage is determined by the highest level histologic evidence that is available. Following preoperative therapy (such as chemotherapy and radiation), subsequent pathologic staging is associated with the prefix "y". Thus a patient with ipsilateral nodal metastases might be downstaged by preoperative chemotherapy

from pN2 prior to treatment to ypN0 after pathologic analysis of the post-chemotherapy surgical specimen.

In common with most other solid malignancies, lung cancer staging is defined by the local extent of the primary tumor (T), involvement of associated lymph nodes (N), and whether or not metastases (M) exist. The TNM classification for lung cancer was originally proposed by Mountain in the early 1970s based on an analysis of 2,155 surgically resected patients at the MD Anderson Cancer Center (MDACC). This staging system was adopted by the American Joint Committee on Cancer (AJCC) in 1973 and by the Union Internationale Contre le Cancer (UICC) the following year. In 1997, Mountain refined the staging system based on analysis of an expanded dataset, which included 5,319 surgically treated patients collected from the MD Anderson Cancer Center between 1975 and 1988 and the North American Lung Cancer Study Group between 1977 and 1982 [1]. The sixth iteration of the lung cancer staging system was in 1997. At the time it was clear that there were significant limitations with the staging system. First, the system was based almost exclusively on outcome analysis of patients who underwent surgical resection, a subset of patients, which represents a small proportion of the population of patients with lung cancer. Second, the stage classifications were based on analysis of a relatively small number of patients, so there were small populations of patients and whose stage assignment was frequently based on intuition rather than data-derived evidence. Third, most patients in the analysis came from a single academic institution, and all were treated at North American centers; thus, the relevance and applicability to patients with lung cancer in other geographic regions was uncertain. Acknowledging these limitations, the International Association for the Study of Lung Cancer (IASLC) convened a lung cancer staging workgroup in 1998 and collected data on a total of 100,869 patients from multiple institutions worldwide [2]. The database included lung tumor cases diagnosed between 1990 and 2000, a relatively short time interval during which staging methods have remained fairly consistent and that allowed at least 5 years of follow-up

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before analysis. Ultimately, there were a total of 81,015 analyzable cases from 46 institutions in 19 countries of which 67,725 were non-small cell lung cancer, 13,290 were small cell lung cancer, and 513 were carcinoid tumors. The IASLC published their staging analyses in a series of publications in 2007 [3–6], and the data were externally validated using the population-based Surveillance, Epidemiology and End Results (SEER) cancer registry data [3]. In January 2010, the revised staging criteria for tumor (T) and metastases (M) were officially adopted by the 7th edition of the American Joint Commission on Cancer (AJCC) and the International Union Against Cancer (UICC) Staging Manual.

The Revised TNM Staging System for Non-small Cell Lung Cancer (AJCC 7th Edition)

Based on the findings of the IASLC Staging Project, a number of changes were incorporated into the previous staging system (AJCC 6th edition). These included changes in the criteria for T and M staging; however, no changes were adopted for nodal (N) staging (Table 2.1). The major differences in T-stage included changes in the stage assignment based on size. Major cutoff points that portended changes in outcome were seen for tumors at 2, 3, 5, and 7 cm. Thus, T1 tumors are now subclassified as T1a (tumor ≤ 2 cm) and T1b (tumor >2 and ≤ 3 cm), T2 tumors as T2a (tumor >3 and ≤ 5 cm) and T2b (tumor >5 and ≤ 7 cm), and T3 (tumor >7 cm), which in the previous AJCC 6th edition was included in the T2 group. Furthermore, changes in the classification of satellite nodules and ipsilateral, different-lobe nodules were made. Because of an observed improved survival over T4 tumors (by direct invasion), homo-lobar satellite nodules were reclassified as T3, and hetero-lobar, ipsilateral nodules (previously, M1) were reclassified as T4 [5]. The revisions included in the AJCC 7th edition staging system did not affect other previous anatomic determinates of tumor stage such as visceral pleural involvement, invasion of a major bronchus, post-obstructive atelectasis, and invasion of the carina, mediastinum, or other organs by direct extension. These factors retain their prognostic significance and stage assignment (Table 2.1).

The IASLC also recommended changes to the staging of metastases (M). Major results from their analysis included the finding that patients with metastases outside the thorax had worse survival than those with metastases confined to the chest. Thus, the AJCC 7th edition now divides the M1 descriptor into M1a (intrathoracic metastases) and M1b (extrathoracic metastases). In addition, patients with ipsilateral pleural effusion (T4/stage IIIB in the AJCC 6th edition) have been found to have survival similar to patients with M1a metastases and are now classified as such (stage IV) [4].

And, as described previously, patients with hetero-lobar, ipsilateral nodules (previously, M1) have been reclassified as T4 (stage IIIB instead of stage IV) to reflect prognosis superior to that of patients with metastatic disease.

The IASLC also examined nodal stage, and though significant changes in survival were noted between patients with single-zone N1 and multi-zone N1 metastases and between single-zone N2 and multi-zone N2 metastases, because these survival differences did not maintain significance independent of T-stage, no revisions in the nodal staging system were recommended (Fig. 2.1). Nonetheless, it is worthwhile noting that extent of nodal involvement within a given N class did appear to influence survival with nodal metastases to multiple zones adversely impacting survival compared to single-zone disease [6]. Patients with a single N1 nodal zone involved fared the best, whereas patients with multiple positive N2 zones had very poor survival. Interestingly, however, patients with a single N2 zone involved had similar survival to patients with multiple N1 zones.

Significance of the Revised TNM Classification System for Non-small Cell Lung Cancer (AJCC 7th Edition)

The clinical utility of the revised staging system for non-small cell lung cancer has been evaluated by several investigators [7–9]. A group of 1,154 patients who had undergone complete surgical resection for NSCLC at the University of Texas, MD Anderson Cancer Center, was retrospectively classified according to both the AJCC 6th edition and 7th edition staging systems. The AJCC 7th edition staging system was more effective at ordering and differentiating patients ($p=0.009$) [10]. In addition, we found that the application of AJCC 7th edition to patients previously staged by AJCC 6th edition resulted in a change in overall stage assignment in 17.5 % of cases, with the most common stage shifts consisting of patients being upstaged from stage IB to IIA and downstaged from IIIB to IIIA (Table 2.2). This has implications with respect to treatment assignment, as patients with stage II NSCLC are generally treated with adjuvant chemotherapy, and surgery may be recommended for patients with stage IIIa disease but is generally contraindicated for stage IIIB tumors. In a similar manner, Suzuki and colleagues applied both AJCC 6th and the revised TNM systems to 1,623 patients who underwent lung cancer resection [11]. Better separation of stage survival curves were seen using the revised TNM system as well as an increase in the proportion of patients with stage IIA, IIB, IIIA, and IV tumors and a decrease in the numbers of patients with stage IB and IIIB disease. The largest shifts occurred in upstaging of IB to IIA and downstaging of IIIB to IIIA. Lyons and colleagues have

Table 2.1 Tumor, node, and metastases (TNM) definitions

<i>Primary tumor (T)</i>	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) ^a
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 cm but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina ^a but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe
<i>Regional lymph nodes (N)</i>	
NX	Regional lymph nodes cannot be assessed
N0	No regional node metastases
N1	Metastases to ipsilateral peribronchial and/or ipsilateral hilar node(s) and intrapulmonary nodes, including involvement by direct extension
N2	Metastases to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular node(s)
<i>Distant metastasis (M)</i>	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion ^b
M1b	Distant metastasis (in extrathoracic organs)

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^aThe uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a

^bMost pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0

reported similar results [12]. In an analysis of 414 surgical cases, 18 % of patients had a change in stage designation after application of the revised TNM staging system, with 6 % of patients downstaged (mainly from IIIB) and 12 % upstaged (mainly from stage IB).

Noninvasive Staging of Lung Cancer

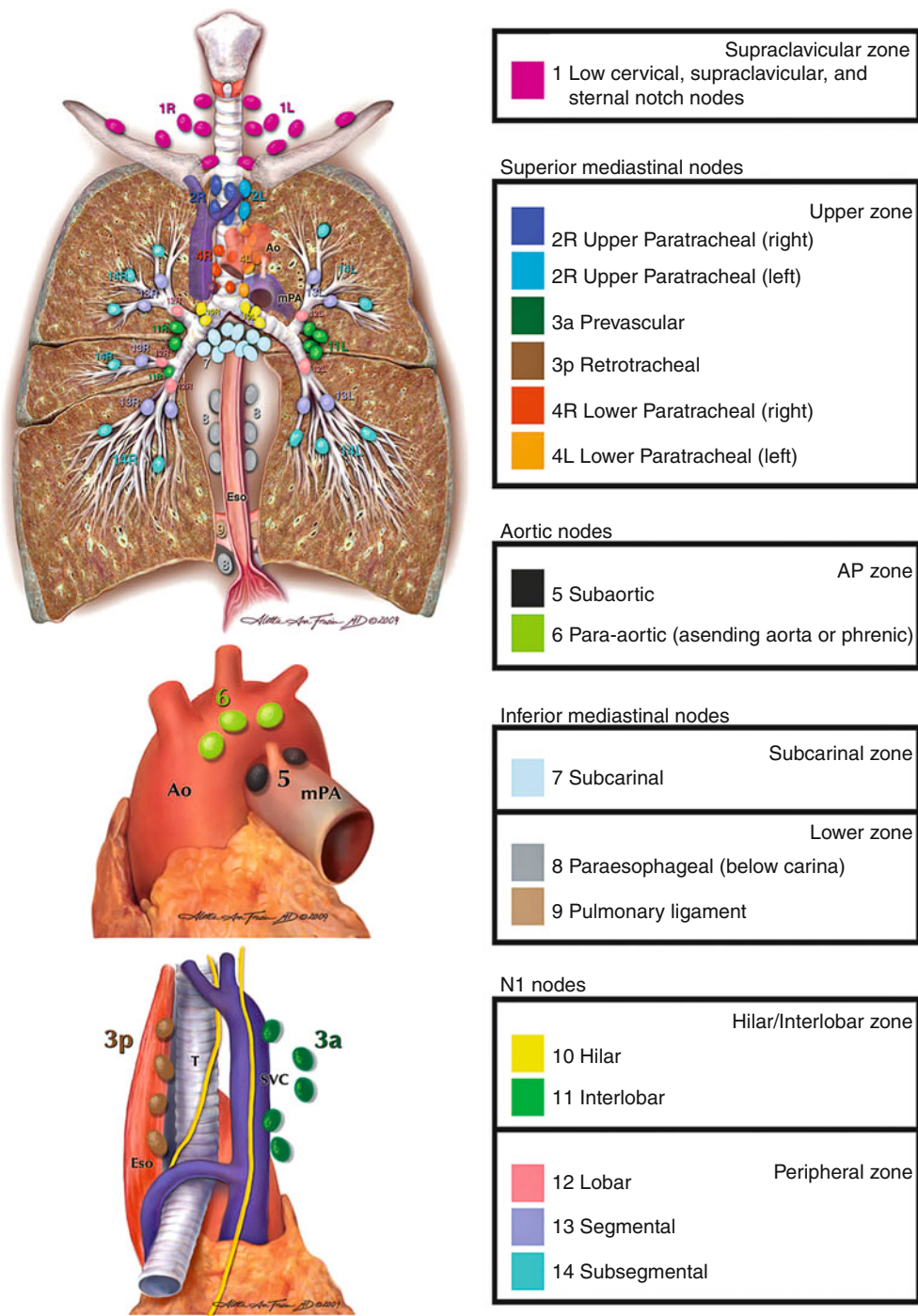
Computed Tomography

Computed tomography (CT) is usually the initial imaging modality used to define the anatomic extent of lung cancer. It provides not only staging information but also provides information about anatomic relationships that are important for surgical or radiation therapy planning. CT scans for lung

cancer staging should be contrast enhanced to define anatomic relationships between the tumor and the mediastinal and pulmonary vessels and also to visualize mediastinal and hilar lymph nodes [13]. CTs should be performed at a minimum of 3.75-mm collimation (slice thickness) and should extend from the supraclavicular region to below the kidneys to allow for visualization of supraclavicular lymph nodes, both adrenal glands, and the majority of the liver [14].

CT scans can provide rough information about tumor size, but at the stage-determining cut points (e.g., 3, 5 and 7 cm), it is not sufficiently sensitive to determine T-stage. However, at the extremes of tumor size, T-stage may be reliably predicted [15]. Thus, a tumor measuring 1 cm on CT will most likely be a true T1 tumor at pathology, and a 10 cm tumor will likely be a T3 tumor. For tumors that abut the surface of the lung, CT cannot reliably determine visceral

Fig. 2.1 The International Association for the Study of Lung Cancer (IASLC) lymph node map, including the proposed grouping of lymph node stations into “zones” for the purposes of prognostic analyses



pleural invasion, and so the differentiation of T1 from T2 (by visceral pleural invasion) is not possible, though pleural puckering is often suggestive of visceral pleural invasion. Chest wall invasion is often obvious on CT but may also be subtle enough to not be detected except at the time of surgery. Tumors extending into tissue outside of the chest wall or rib erosion are usually reliable predictors of chest wall invasion (T3), and the accuracy of CT for predicting chest wall invasion has been reported to be only 39–87 % [16, 17]. Invasion of mediastinal structures such

as the esophagus, mediastinal fat, pericardium, and trachea can similarly be imprecise on CT unless there is extensive invasion. Generally, additional confirmatory tests will be required to establish invasion such as bronchoscopy, esophagoscopy, and esophageal (EUS) or endobronchial ultrasound (EBUS), and clinical findings such as phrenic nerve paralysis or intrascapular pain (suggestive of aortic involvement) can aid in establishing T4 status when coupled with CT findings. Invasion of the spine can often be diagnosed if bone destruction is evident; however, early

Table 2.2 TNM stage groupings

Anatomic stage/prognostic groups			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
Stage IIB	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
Stage IV	T4	N3	M0
	Any T	Any N	M1a
	Any T	Any N	M1b

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invasion may be missed. In cases of suspected spine involvement, magnetic resonance imaging (MRI) complements CT imaging in assessing vertebral invasion. In a prospective study by Webb, CT was able to discriminate between advanced-stage (T3/T4) and early stage lung cancers (T1/T2) with a sensitivity, specificity, and accuracy of 84, 70, and 78 %, respectively [17].

CT can readily identify noncalcified nodules in other lobes but does not provide pathologic diagnosis. Therefore, unless different-lobe nodules are obviously metastatic, their histology should be determined if they would change stage assignment. In the case of larger nodules (>1 cm), this can usually be easily accomplished via percutaneous CT-guided biopsy or navigational bronchoscopic biopsy. Frequently, however, the clinician is faced with multiple small nodules or ground-glass opacities (GGO) that are impossible to biopsy without video-assisted thoracoscopy (VATS) and maybe even thoracotomy. The judgment of the clinician is required to decide whether to pursue histologic sampling or not and whether their presence will influence definitive therapy.

CT and Mediastinal Nodal Staging

By convention, a cutoff point of 1 cm or greater is used to differentiate a potentially metastatically involved node from a noninvolved node. Unfortunately, the accuracy of CT for predicting metastases to the mediastinal nodes is low, the false-positive rate of CT in the diagnosis of nodal metastases is between 15 and 80 % [18], and the false-negative rate is as high as 12 % [19–21]. A recent meta-analysis by Toloza et al. included 3,438 patients from 20 studies and found that pooled sensitivity and specificity of CT scanning was 57 and 82 %, respectively, with a positive predictive value of only 56 % [22]. An inherent limitation of CT prediction of nodal metastases is that lymph node size is not a reliable indicator of nodal metastatic disease. In a recent analysis of 256 patients (2,891 nodes), Prenzel and colleagues reported that at least 77 % of patients without nodal metastases had at least one lymph node greater than 1 cm in diameter. Furthermore, 12 % of patients with N2 metastases had no enlarged nodes on CT scanning [23].

Positron Emission Tomography (PET)

A major advance in the preoperative staging of lung cancer has been the development of positron emission tomography (PET). PET works by taking advantage of the fact that cancer cells and cells with high metabolic activity have increased cellular uptake of glucose and increased rates of glycolysis. Radiolabeled fluorodeoxyglucose (FDG), a glucose analog, undergoes uptake by cancer cells but following phosphorylation is unable to undergo further metabolism and is retained intracellularly. The intensity of FDG uptake can be quantified (standardized uptake value or SUV) and is considered abnormal if greater than 2.5 or if it is above the normal background uptake in the mediastinum [24]. PET provides information about the metabolic activity of a lesion, but its spatial resolution is poor compared to the precise anatomic information that CT can provide [24, 25]. The development of integrated PET/CT scanners where 2D axial CT images are co-localized with colorized PET data has enabled more accurate assessment of location of metabolic activity than either modality when performed separately [26]. It should be noted that the CT component of most integrated PET/CT scans is performed without intravenous contrast, making detailed information about the relationships of pulmonary vasculature to tumors or mediastinal and hilar nodes not possible. Furthermore, as the CT is performed without breath holding, the lung parenchyma is underinflated and subject to motion artifact which obscures detail. This is particularly relevant when evaluating small (<5 mm) intraparenchymal nodules.

PET/CT rarely provides additional information regarding T-stage over what is available from a contrast-enhanced CT, though there is some evidence to suggest that the level of FDG uptake may offer prognostic information regarding survival [24]. Its main role in the staging and pretreatment assessment of lung cancer lies in its ability to predict mediastinal nodal and distant metastases.

PET/CT and Mediastinal Staging

PET/CT has significantly improved our ability to predict the presence of metastatic disease in mediastinal nodes. CT is limited by the fact that patients can have enlarged mediastinal nodes without metastatic involvement, and conversely, cancer can involve nodes without necessarily causing their enlargement (defined as >1 cm in short axis dimension). PET, however, relies on metabolic activity of tissue rather than on anatomic size criteria and thus has an advantage over CT in this regard. Standardized quantitative criteria for an abnormal PET scan finding in the mediastinum have not been defined; however, an SUV > 2.5 or uptake greater than the background activity of lung or liver is frequently used [27]. False positivity may occur with inflammatory tissue. Thus, patients with granulomatous inflammation or infection may have nodes with increased FDG uptake leading to falsely positive scans. Furthermore, there must be a critical mass of FDG-avid tissue to allow its detection, thus nodes with only microscopic involvement with metastases will not appear FDG avid. The spatial resolution with current generation PET scanners is about 7 mm. Accordingly, an FDG-avid node smaller than this is generally highly suspicious for metastatic involvement, whereas a non-avid node may still harbor tumor. A recent analysis of 2,865 patients with lung cancer demonstrated a pooled sensitivity and specificity of 74 and 85 %, respectively [28]. Most studies have reported negative predictive values of 90 % or greater, and in general, a patient with a negative PET scan and a peripheral lung cancer may proceed to definitive therapy without further evaluation of the mediastinum. The American College of Surgeons Oncology Group (ACOSOG) ZD0050 trial prospectively evaluated the use of PET (not integrated PET/CT) in the preoperative staging and work-up of patients with proven lung cancer [29]; 303 patients were enrolled in the study, of which 76 % were clinical stage I prior to PET scanning. PET identified unsuspected metastatic disease in 6 %; however, PET overdiagnosed metastatic disease in 7 % of patients who were subsequently found to be without metastases. PET identified 82 of 302 (27 %) patients as having N2/3 disease; however, only 46/82 (56 %) were true positives (positive predictive value = 56 %, negative predictive value = 87 %). Overall, PET identified 61 (20 %) patients in whom nontherapeutic thoracotomy could poten-

tially be avoided. There was a relatively high rate of false positives in this study (44 %), which strongly argues in favor of histologic confirmation of PET-positive mediastinal nodes. Indeed, both the American College of Chest Physicians and the European Society of Thoracic Surgeons recommend mediastinal nodal sampling to confirm PET-positive mediastinal nodes.

Patients with small peripheral lung cancers that have negative nodes by PET and CT criteria may safely undergo either surgical resection or ablative therapy as their physiologic performance allows. The incidence of occult N2 metastases in this group of patients is between 5 and 11 % [30–32]. Patients with central tumors, however, are at significantly higher risk for occult N2 disease. In a study by Lee et al., patients with peripheral tumors smaller than 2 cm and a radiologically negative mediastinum had a 3 % incidence of occult N2 nodal metastases but increased to 22 % if the tumor was centrally located [33]. The incidence of occult N2 disease increased substantially for tumors that were greater than 2 cm and centrally located and approached 30 %. Thus, even patients who have negative mediastinal nodes by PET and CT should be considered for histologic assessment of the mediastinal nodes if they have central tumors that are greater than 2 cm in size. The same applies to cases where the risks of surgery are great and the marginal benefit of an operative approach would be greatly offset by the presence of occult nodal disease, examples might include patients who require pneumonectomy, resection of Pancoast tumors, and patients with severe comorbidities or of extremely advanced age.

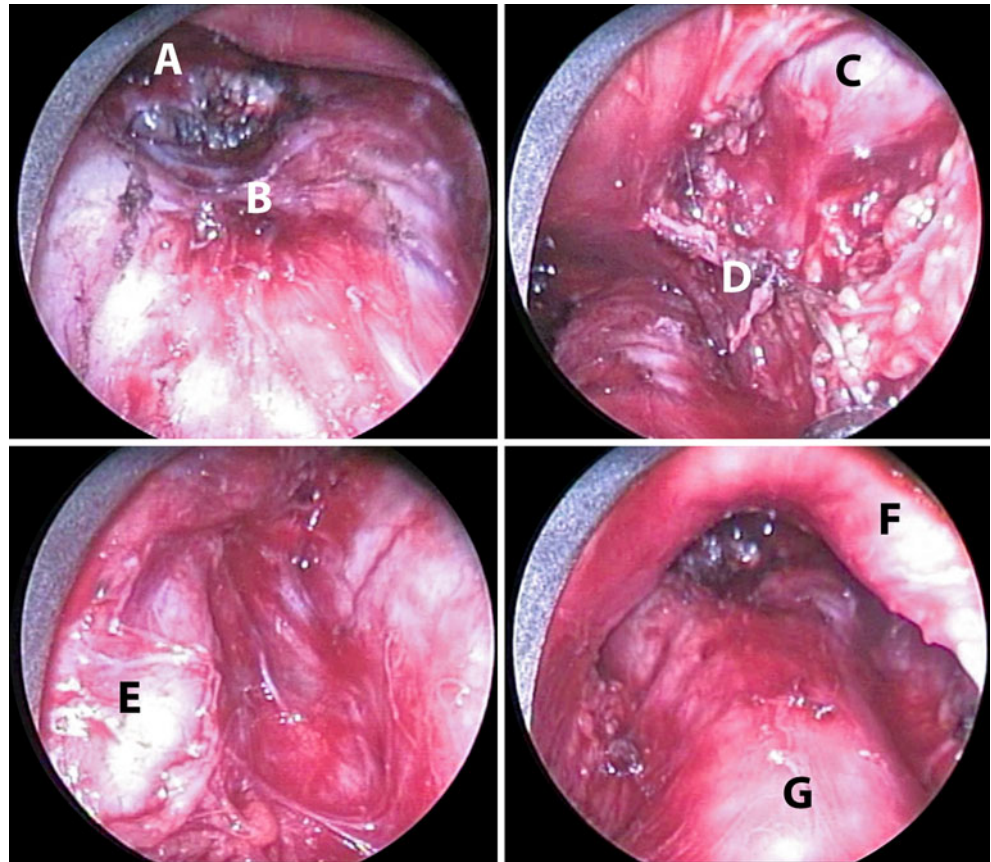
Invasive Staging for Lung Cancer

Invasive surgical staging is generally performed either with surgery (mediastinoscopy, anterior mediastinotomy [Chamberlain procedure], or VATS lymph node sampling) or via endoscopy (transbronchial needle aspiration, with or without endobronchial ultrasound [EBUS] guidance, and esophageal ultrasound [EUS] fine-needle aspiration). Occasionally transthoracic CT-guided biopsy may be performed to sample nodes not immediately adjacent to the tracheobronchial or esophageal structures and therefore inaccessible to mediastinoscopy or endoscopic methods.

Cervical Mediastinoscopy

Cervical mediastinoscopy (CM) was first described by Carlsens at the Karolinska Institute, Sweden in 1959 [34]. It has remained the gold standard method of histologic sampling of mediastinal nodes since then but will likely be replaced by less invasive endoscopic methods, as a growing

Fig. 2.2 Videomediastinoscopy. The following mediastinal structures are visible:
A – subcarinal lymph node with right main pulmonary artery overlying; *B* – carina; *C* – superior vena cava; *D* – azygos vein; *E* – left recurrent laryngeal nerve; *F* – innominate artery; *G* – distal trachea



body of literature suggests similar efficacy of EBUS and EUS [35]. Mediastinoscopy is performed as an outpatient surgery under general anesthesia and is now more commonly performed with a videomediastinoscope, which greatly improves visualization [36]. The patient is placed in a supine position, and a 2-cm transverse incision is placed 1 cm above the suprasternal notch. The platysma is divided and the strap muscles separated in the midline, exposing the underlying anterior surface of the trachea. Incision of a thin layer of investing fascia allows entry into the avascular pre-tracheal space. The mediastinoscope is then directed into this space under direct vision. Further dissection is performed bluntly with the aid of a suction/cautery device. The development of the videomediastinoscope significantly enhanced visualization and now allows for extremely accurate dissection and nodal sampling (Fig. 2.2). The mediastinoscope can readily access stations 2R, 2L, 4R, 4L, and 7, and attempts to sample nodes from these stations should be made. It is extremely unusual not to be able to sample nodal tissue from the 4R, 4L, and 7 stations in nearly every patient. Nodes in the 2L region are not infrequently absent or diminutive. Furthermore, excessive dissection in the left paratracheal region does place the left recurrent laryngeal nerve at potential risk for traction injury, so judgment is required whether to persist in the pursuit of small, high left paratracheal nodes.

With extensive dissection distally, nodes in the 10L and 10R stations may be occasionally accessed, though this is not routinely performed (Table 2.3).

Mediastinoscopy has been shown to be highly accurate for detecting N2 and N3 metastases. In a large single-institution series from Duke Medical Center, Lemaire and colleagues reported a sensitivity of 86 % and a negative predictive value (NPV) of 95 % [37]. A meta-analysis of 5,687 patients found similar results with a sensitivity and NPV of 81 and 93 %, respectively [38]. However, these results may reflect outcomes at specialized centers. Little and colleagues reported results from a large American College of Surgeons database that recorded patterns of surgical care among more than 11,000 patients with lung cancer. Mediastinoscopy was performed in only 27 % of cases, and among these, nodal tissue was present in the final pathological report in only 47 % of cases. This suggests that in practice mediastinoscopy is not only infrequently performed but inadequate for staging more than half of the time. A visual inspection of the peritracheal soft tissue is insufficient for staging purposes, and nodal tissue must be obtained from the paratracheal and subcarinal regions in all cases.

Structures at risk for injury during mediastinoscopy include the ascending aorta, superior vena cava, azygos vein, trachea, bronchi, left recurrent laryngeal nerve, right main

Table 2.3 IASLC definition of intrathoracic nodal stations

Nodal station	Description	Definition
Level 1 (left/right)	Low cervical, supraclavicular, sternal notch	<i>Upper border:</i> lower margin of cricoid cartilage <i>Lower border:</i> clavicles bilaterally, in the midline, the upper border of the manubrium
Level 2 (left/right)	Upper paratracheal nodes	2R: <i>Upper border:</i> apex of the lung and pleural space, midline, the upper border of the manubrium <i>Lower border:</i> intersection of the caudal margin of innominate vein with the trachea 2L: <i>Upper border:</i> apex of the lung and pleural space, midline, the upper border of the manubrium <i>Lower border:</i> superior border of the aortic arch
Level 3	Prevascular and retrotracheal nodes	3a: Prevascular <i>On the right</i> <i>Upper border:</i> apex of chest <i>Lower border:</i> level of carina <i>Anterior border:</i> posterior sternum <i>Posterior border:</i> anterior to superior vena cava <i>On the left</i> <i>Upper border:</i> apex of chest <i>Lower border:</i> level of carina <i>Anterior border:</i> posterior sternum <i>Posterior border:</i> left carotid artery 3p: Retrotracheal <i>Upper border:</i> apex of chest <i>Lower border:</i> level of carina
Level 4	Lower paratracheal nodes	4R: paratracheal and pretracheal nodes extending to the left lateral border of the trachea <i>Upper border:</i> intersection of caudal margin of innominate vein with the trachea <i>Lower border:</i> lower border of azygos vein 4L: left of the left lateral border of the trachea, medial to the ligamentum arteriosum <i>Upper border:</i> upper margin of the aortic arch <i>Lower border:</i> upper rim of the left main pulmonary artery
Level 5	Subaortic/aortopulmonary nodes	Subaortic nodes lateral to the ligamentum arteriosum <i>Upper border:</i> the lower border of the aortic arch <i>Lower border:</i> upper rim of the left main pulmonary artery
Level 6	Para-aortic nodes (ascending aorta or phrenic)	Nodes anterior and lateral the ascending aorta and aortic arch <i>Upper border:</i> tangential line to the upper aspect of the aortic arch <i>Lower border:</i> the lower border of the aortic arch
Level 7	Subcarinal	<i>Upper border:</i> the carina <i>Lower border:</i> Left: the upper aspect of the lower lobe bronchus on the left Right: the lower border of the bronchus intermedius
Level 8 (left/right)	Paraesophageal nodes (below the carina)	Nodes adjacent to the wall of the esophagus and to the right or left of the midline excluding subcarinal nodes <i>Upper border:</i> Left: the upper border of the lower lobe bronchus Right: lower border of the bronchus intermedius on the right <i>Lower border:</i> the diaphragm
Level 9 (left/right)	Pulmonary ligament nodes	Nodes within the pulmonary ligament <i>Upper border:</i> the inferior pulmonary vein <i>Lower border:</i> the diaphragm
Level 10 (left/right)	Hilar nodes	Nodes immediately adjacent to the main stem bronchus and hilar vessels including proximal portion of the pulmonary vein and the main pulmonary artery <i>Upper border:</i> Right: the lower aspect of the azygos vein Left: the upper aspect of the pulmonary artery <i>Lower border:</i> Interlobar region bilaterally

Table 2.3 (continued)

Level 11 (left/right)	Interlobar nodes	Between the origin of the lobar bronchi
Level 12	Lobar nodes	Adjacent to the lobar bronchi
Level 13	Segmental nodes	Adjacent to the segmental bronchi
Level 14	Subsegmental nodes	Adjacent to the subsegmental bronchi

pulmonary artery, innominate artery, right pleura, and esophagus. Despite this, the procedure is extremely safe with a reported risk of death as low as 0.05 % in specialized centers. Reported rates of morbidity include recurrent laryngeal nerve palsy (0.55 %), hemorrhage (0.32 %), tracheal injury (0.09 %), and pneumothorax (0.09 %) [37].

Extended Mediastinoscopy

The prevascular and subaortic regions are inaccessible to conventional mediastinoscopy but may be accessed by what is termed “extended mediastinoscopy” (ECM) [39]. Using the standard cervical incision for CM, blunt dissection is performed anterior to the arch of the aorta between the innominate artery on the right and the left carotid artery on the left. A mediastinoscope can be passed into the preaortic area to biopsy nodes at the level 5 and 6 stations. Sensitivity and negative predictive values as high as 75 and 94 %, respectively, have been reported with selective use of ECM.

Anterior Mediastinotomy

The main indication to perform anterior mediastinotomy (also known as a Chamberlain procedure) is to access nodes or tumor in the prevascular regions (station 3a on the right and 5 and 6 on the left), areas that are beyond the reach of conventional mediastinoscopy [40]. The technique involves either a left- or right-sided transverse parasternal incision (usually 4–5 cm in length) with either resection of the second costal cartilage or an incision in the second or third intercostal space. The parietal pleura is swept laterally using blunt dissection. Occasionally, the internal mammary artery is encountered and must be ligated, though it is preferable to avoid it altogether. For this reason, prior use of an ipsilateral mammary artery for coronary artery bypass grafting is a relative contraindication for anterior mediastinotomy. Sensitivity of the procedure is approximately 80–90 % with a false-negative rate of about 10 %.

Video-Assisted Thoracoscopy

Video-assisted thoracoscopy (VATS) has been championed by several authors as being useful for evaluation of aortopulmo-

nary window nodes. It has the advantage of providing excellent visualization and being able to resect essentially all tissue in the aortopulmonary window, thus providing a highly accurate way of assessing nodal involvement. In addition to paratracheal and subcarinal nodes, VATS can sample nodes in the inferior pulmonary ligament and paraesophageal regions that are beyond the scope of CM. Furthermore, visualization of the entire pleural cavity is useful for identification of occult pleural metastases. Landreneau and colleagues reported a sensitivity and specificity of 100 % in a small series of patients with enlarged aortopulmonary window, peri-azygos, and subcarinal nodes [41]. Cerfolio and colleagues found that left-sided VATS was more accurate than either EUS or anterior mediastinotomy for suspected nodes in the aortopulmonary window [42]. The chief disadvantage of the procedure is that it requires single-lung ventilation and usually an overnight hospitalization.

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) can be useful for biopsying mediastinal nodes (especially the subcarinal station) at the time of bronchoscopy. The procedure requires a therapeutic bronchoscope with a working channel large enough to pass a flexible 19- or 22-gauge needle and its sheath [43, 44]. Nodes in the subcarinal region can be easily biopsied, but because the technique is blind, relying on an estimation of the site of nodes from CT imaging, it is much less reliable for paratracheal nodes unless they are quite enlarged. The technique has been shown to be highly operator dependent with reported sensitivity rates ranging from 37 to 89 %. Because of these technical limitations, a recent American College of Chest Physicians practice survey reported that the technique was routinely used by only 12 % of pulmonologists [45]. In an effort to improve the sensitivity of TBNA, Herth and colleagues investigated the use of concomitant radial probe ultrasound for localization of lymph nodes at the time of TBNA to improve accuracy [46]. In 200 patients with enlarged mediastinal nodes and proven or suspected lung cancer, use of radial probe ultrasound immediately prior to TBNA improved sampling sensitivity for paratracheal nodes from 58 to 84 % ($p < 0.001$) but not for nodes in the subcarinal region (74 % vs 86 %, $p = \text{NS}$) [47]. The improved sensitivity achieved by coupling ultrasound imaging with TBNA led to the development of the integrated linear endobronchial ultrasound bronchoscope, which has now radically changed how we currently stage the mediastinum.

Endobronchial Ultrasound Transbronchial Needle Aspiration

Over the last decade endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) has rapidly gained acceptance as a method of histologically sampling the mediastinal lymph nodes in patients with lung cancer or other causes of mediastinal adenopathy. The technique is performed using a modified bronchoscope with a linear ultrasound array at its working end and a flexible 22-gauge needle and sheath that exits the working channel of the bronchoscope at 30° to the scope axis (Fig. 2.3). The ultrasound array provides real-time 2D image guidance so that both peritracheal and peribronchial nodes may be biopsied (Figs. 2.4 and 2.5). The procedure is usually performed (for staging purposes) under general anesthesia although it may also be done with sedation and topical anesthesia, particularly if biopsy of only a single nodal station is anticipated. EBUS-TBNA can sample paratracheal nodes (stations 2 and 4), subcarinal nodes (station 7), and hilar nodes (stations 10 and 11), the latter which are usually beyond the reach of cervical mediastinoscopy. Its clinical utility for staging lung cancer was initially described by Yasafuku in 2004 [48]: 102 patients with proven or suspected lung cancer underwent staging with CT, PET, and EBUS. EBUS identified 24 patients with N2 metastases and with only 2 false negatives and had higher sensitivity and negative predictive value than PET scanning (92 % vs 80 %, 97 % vs 92 %, respectively) [49]. Numerous studies have since confirmed the accuracy of EBUS, and two recent meta-analyses have shown pooled sensitivity rates of between 88 and 93 % [50, 51]. Even in patients with a negative mediastinum on 2D and metabolic imaging, PET has shown benefit in detecting occult mediastinal nodes. Herth and colleagues performed EBUS on 97 patients with lung cancer who had a negative mediastinum by PET and CT scanning [52]. EBUS identified occult N2 disease in five patients and unsuspected N3 disease in one patient. An additional two patients were found to have occult N1 nodes. Altogether EBUS upstaged 8 % of patients. Three studies have compared the accuracy of EBUS to that of mediastinoscopy (CM) for staging the mediastinum in lung cancer. Ernst and colleagues performed EBUS-TBNA followed by CM on 66 patients with lung cancer and mediastinal adenopathy [53]. The diagnostic yield of EBUS was higher than CM (91 % vs 78 %, $p=0.007$), and the main difference was in a better ability of EBUS to obtain diagnostic tissue from the subcarinal station. However, on a per patient basis, there was no statistical difference between EBUS and CM in defining the true N-stage. A Dutch study performed a randomized trial comparing up-front CM to EBUS plus EUS (esophageal ultrasound) staging followed by CM only if endoscopic staging was negative. In this study that included 241 patients, endoscopic staging and CM had similar false-negative rates (8 and 9 %, respectively)

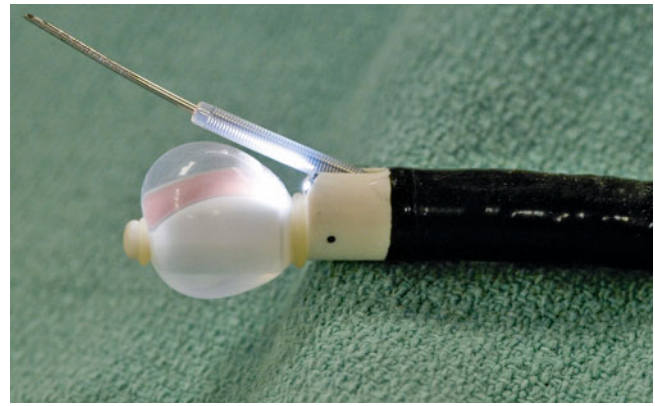


Fig. 2.3 The linear endobronchial ultrasound scope (Olympus Corp, BF-UC180F). The curvilinear ultrasound probe is covered with a saline-filled balloon to aid acoustic coupling with the tracheal wall. A 22-gauge needle and sheath exits the bronchoscope at 30° off-axis

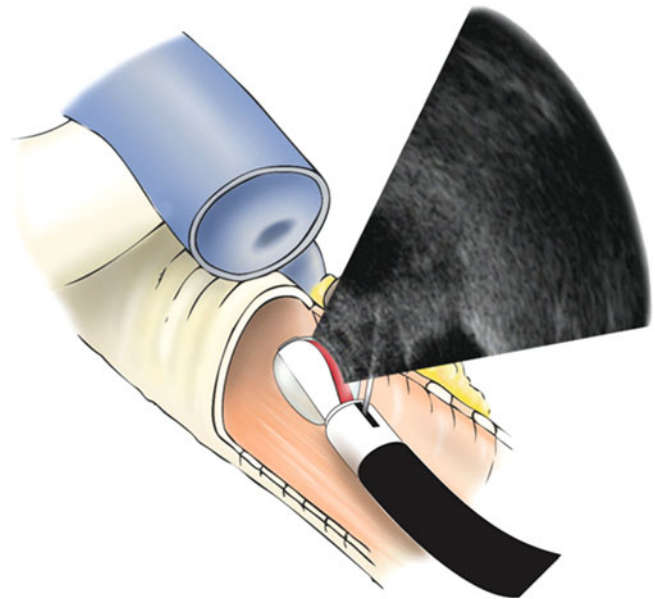


Fig. 2.4 The EBUS scope is passed perorally into the trachea. The node of interest is visualized with ultrasound, and a needle is placed into the node under real-time image guidance

and similar sensitivity and negative predictive values (85 % vs 80 % and 84 % vs 86 %, respectively; $p=NS$); however, the combination of endoscopic staging and selective use of CM had a sensitivity of 94 %, significantly higher than either CM or endoscopic staging alone [54]. Lastly, a recently published prospective case-control study by Yasafuku and colleagues compared EBUS-TBNA to CM in 153 patients [55]. Though CM examined more nodes per patient compared to EBUS-TBNA (4 vs 3) and more nodes overall (573 vs 426), there were no significant differences in sensitivity rates (79 % vs 81 %) and negative predictive values (90 % vs 91 %). We may conclude, therefore, that EBUS-TBNA appears to be as accurate as CM at staging the mediastinum in patients with lung cancer.



Fig. 2.5 EBUS-TBNA showing the needle inside a left paratracheal node. The round, hypoechoic structure at the bottom of the picture is the left main pulmonary artery

Esophageal Ultrasound (EUS)

Endoscopic esophageal ultrasound (EUS) offers the ability to sample lymph nodes that are not contiguous with the tracheobronchial tree and therefore offers an attractive complement to EBUS to allow “total” endoscopic staging of the mediastinum. EUS can access lymph nodes in the left paratracheal (station 4L), subcarinal (station 7), paraesophageal (station 8), and inferior pulmonary ligament (station 9) regions [56]. Occasionally, nodes in the aortopulmonary window (stations 5/6) may also be sampled. Several comparative studies have shown that EUS has similar sensitivity as EBUS-TBNA in assessment of mediastinal nodes [57, 58]; however, the combination of EBUS and EUS appears to be more accurate than either procedure alone. In a prospective study of 33 patients with lung cancer, Villman and colleagues performed EBUS and EUS and showed an accuracy of 89 and 86 %, respectively [59]. However, the combined accuracy of both procedures was 100 %. Similarly, Wallace et al. performed EBUS and EUS in 138 consecutive patients with lung cancer [60]. The sensitivity and negative predictive value for both procedures was identical – 69 and 88 %, respectively. Combined sensitivity and NPV were 93 and 97 %.

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