In 2010, the most recent year for which numbers are available, there were 201,144 new cases of lung cancer (107,164 men and 93,984 women) in the United States. With 158,248 deaths, lung cancer remains the leading cause of cancer-related deaths in both men and women. Of newly diagnosed cases, approximately 80% will be non–small cell lung cancer (NSCLC), and of these, 80% will involve metastatic or locally advanced disease. Only 20% will be in potentially surgically curable patients with early-stage disease, where complete resection yields 5-year survivals of 40% to 75%.

Careful staging of newly diagnosed lung cancer is critical for several reasons. First, determining the patient’s clinical TNM (tumor, nodes, metastasis) stage allows appropriate therapeutic decisions to be made on the basis of the specific stage of disease. This is particularly important for locally advanced disease in which multimodality therapy (induction or adjuvant) is standard care, as well as for metastatic disease when surgery should be avoided. Second, accurate staging allows the clinician to give the patient valuable prognostic information. Third, staging allows evaluation of new therapeutic interventions, and comparison of results of treatments between studies and institutions.

There are controversies about the extent of workup, and the methods used for staging have evolved during the past decade.
Incorporated into the sixth edition of the AJCC and UICC staging manuals. In 1996, the International Association for the Study of Lung Cancer (IASLC) initiated an international staging project to form the basis of the seventh edition of the TNM staging system. The goals of the project were to validate the individual T, N, and M descriptors using a larger database made up of medical and surgical patients from a wide geographic distribution. Data on 100,869 patients, including 67,725 cases of NSCLC, were submitted to the database, and several changes were proposed. The existing N descriptors were validated and not changed (Fig. 16-1). For the T descriptors, size cutoffs were added to the T1 and T2 tumors, and tumors greater than 7 cm in greatest dimension were designated as T3, in light of the prognostic significance of increasing size of the primary tumor (Table 16-1). Additional tumor nodules in the same lobe as the primary, previously known as “satellite nodules,” were reclassified from T4 to T3, and additional nodules in the ipsilateral lung became T4. The M descriptor was divided into M1a (for pleural metastases, malignant effusion, or contralateral pulmonary disease) and M1b (for extrathoracic metastases). After incorporating the suggested changes into

ISBN: 978-0-323-24126-7; PII: B978-0-323-24126-7.00016-8; Author: Sellke & del Nido & Swanson; 00016


Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes
Upper zone
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

Aortic Nodes
AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes
Subcarinal zone
7 Subcarinal

Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament

N, Nodes
Hilar/Interlobar zone
10 Hilar
11 Interlobar

Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

Low cervical, supraclavicular, and sternal notch nodes

Supraclavicular zone

Superior Mediastinal Nodes
Upper zone

Aortic Nodes
AP zone

Inferior Mediastinal Nodes
Subcarinal zone

Lower zone

N, Nodes
Hilar/Interlobar zone

Peripheral zone

Low cervical, supraclavicular, and sternal notch nodes

Supraclavicular zone

Superior Mediastinal Nodes
Upper zone

Aortic Nodes
AP zone

Inferior Mediastinal Nodes
Subcarinal zone

Lower zone

N, Nodes
Hilar/Interlobar zone

Peripheral zone

Low cervical, supraclavicular, and sternal notch nodes

Supraclavicular zone

Superior Mediastinal Nodes
Upper zone

Aortic Nodes
AP zone

Inferior Mediastinal Nodes
Subcarinal zone

Lower zone

N, Nodes
Hilar/Interlobar zone

Peripheral zone
DIAGNOSIS AND STAGING

Diagnosis and clinical staging begin with the initial history and physical examination. A single study may serve the dual purpose of securing a diagnosis and staging the patient. If a patient's treatment is nonsurgical or involves multimodality therapy, obtaining a tissue diagnosis prior to treatment is mandatory. If it appears that the patient's clinical stage will be most appropriately managed by surgical resection alone, tissue confirmation of malignancy can be secured either preoperatively or at the time of exploration, depending on the preference of the operating surgeon.

History and Physical Examination

Patients often come to the surgeon for evaluation with some studies already performed. However, the history and physical examination remain important in the initial evaluation. A detailed history focusing on risk factors—such as duration of cigarette smoking, exposure to asbestos and other industrial hazards, a prior history of lung cancer, and the presence of symptoms—allows the clinician to assess the likelihood of a diagnosis of lung cancer. Bach and associates showed that the duration of tobacco smoking, more so than the amount of daily usage, increases an individual's risk of developing lung cancer.
The lung cancer risk associated with asbestos exposure also increases with the intensity and length of exposure, and together, tobacco use and asbestos exposure have a multiplicative effect. Symptoms, such as bone pain, hoarseness, weight loss, and neurologic changes, can indicate the presence of metastatic disease and direct further investigation.

A physical examination is also important. It provides an estimate of a patient’s overall health status, which influences treatment selection. Physical findings, such as Horner syndrome, or the presence of clubbing, may support the suspicion of lung cancer. Physical examination may also demonstrate advanced disease. For example, palpation of the supraclavicular fossae can reveal lymph node metastases, and auscultation of the lung fields can identify the presence of a malignant pleural effusion.

**NONINVASIVE MODALITIES**

**Chest Radiography**

Posteroanterior and lateral chest radiographs, often done for unrelated reasons, are a common initial study in which a suspected lung cancer is identified. However, most lesions are not visible until they are at least 7 to 10 mm in diameter. A chest radiograph can localize the site of suspect lesions (central or peripheral) and the associated effects of disease, such as atelectasis, consolidation, or proximity to the pleural surface. The presence of a pleural effusion of chest wall invasion or of phrenic nerve involvement causing elevation of the hemidiaphragm may also be seen. Advanced disease may be identified in the case of rib destruction from bone metastases or synchronous lesions in the pulmonary parenchyma. Hilar and mediastinal lymph node metastasis is more difficult to identify, unless there is substantial enlargement.

**Sputum Cytology**

Cytologic analysis of sputum for malignant cells is a simple diagnostic technique but is rarely used in North America because of the epidemiologic shift from centrally located squamous cell to more peripherally located adenocarcinomas. However, sputum cytology is still a potentially relevant test in other parts of the world where squamous cell cancers are more common. Samples may be induced by saline nebulization or collected as a 3-day pool of sputum produced from spontaneous coughing in the morning. Based on 16 published studies of at least 50 patients each, the overall sensitivity is 66% (range, 42% to 97%) and the overall specificity is 99% (range, 68% to 100%). When sputum cytology is used for patients suspected of having lung cancer on clinical grounds, the diagnostic yield is higher, with a sensitivity of 87% and a specificity of 90%.

**Low-Dose Computed Tomography**

An increasing number of patients, particularly in developed countries, now have lung cancers identified by low-dose computed tomography (CT) because of the results of a large prospective U.S. randomized clinical trial. The National Lung Screening Trial (NLST) enrolled 33,454 persons at high risk (participants between ages 55 and 74 years with at least 30 pack years of smoking) for lung cancer at 33 medical centers and randomized them to undergo three annual screenings with either low-dose CT or posteroanterior chest radiography. Patients in the low-dose CT group had a significantly lower risk of death from lung cancer (20% relative risk reduction) and from any cause. The majority (63%) of lung cancers detected by low-dose CT were stage I tumors. The use of low-dose CT will likely increase in the future, largely supplanting chest radiography.

**High-Resolution Computed Tomography**

Once a suspect lesion has been detected on a chest radiograph or a low-dose CT, the next step is a high-resolution CT of the chest and upper abdomen, preferably performed with intravenous contrast. This yields information about the size, characteristics (e.g., spiculation, ground-glass opacification, lack of calcification), and local extent of a potential lung cancer. Potential invasion of contiguous chest wall or mediastinal structures can be assessed.

CT also provides details about the remaining lung parenchyma and pleural spaces. "Satellite" or additional nodules, bullous or emphysematous changes, pleural thickening, masses, or effusion may be identified. The chest CT for a suspected lung cancer should include the upper abdomen, through the liver and adrenal glands. Although most asymptomatic incidental lesions in the upper abdomen are benign (adrenal adenoma, hepatic cysts), unsuspected metastases are identified in a small percentage of patients.

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**TABLE 16-2 Descriptors, Proposed T and M Categories, and Proposed Stage Groupings**

<table>
<thead>
<tr>
<th>Sixth Edition T/M Descriptor</th>
<th>Seventh Edition T/M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (≤2 cm)</td>
<td>T1a</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
<td>IB</td>
</tr>
<tr>
<td>T1 (&gt;2-3 cm)</td>
<td>T1b</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
<td>IB</td>
</tr>
<tr>
<td>T2 (≤5 cm)</td>
<td>T2a</td>
<td>IB</td>
<td>IA</td>
<td>IA</td>
<td>IB</td>
</tr>
<tr>
<td>T2 (&gt;5-7 cm)</td>
<td>T2b</td>
<td>IA</td>
<td>IB</td>
<td>IA</td>
<td>IB</td>
</tr>
<tr>
<td>T3</td>
<td>T3</td>
<td>IB</td>
<td>IA</td>
<td>IA</td>
<td>IB</td>
</tr>
<tr>
<td>T3 invasion</td>
<td>T3</td>
<td>IB</td>
<td>IA</td>
<td>IA</td>
<td>IB</td>
</tr>
<tr>
<td>T4 (same lobe nodules)</td>
<td>T4</td>
<td>IIIA</td>
<td>IIIA</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4</td>
<td>IIIA</td>
<td>IIIA</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td>M1 (ipsilateral lung)</td>
<td>M1</td>
<td>IIIA</td>
<td>IIIA</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td>M1</td>
<td>IIIA</td>
<td>IIIA</td>
<td>III A</td>
<td>III B</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>M1</td>
<td>IIIA</td>
<td>IIIA</td>
<td>III A</td>
<td>III B</td>
</tr>
</tbody>
</table>


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Despite these limitations, PET has become an invaluable tool in lung cancer staging. Several studies have shown that PET is superior to CT in staging the mediastinum in lung cancer patients. Pieterman and colleagues prospectively compared standard staging approaches to PET for detection of mediastinal lymph node and distant metastases in 102 patients with resectable NSCLC who underwent histologic staging of the mediastinum. The sensitivity and specificity of PET for detection of mediastinal nodal metastases were 91% and 86%, respectively, compared with a sensitivity of 75% and a specificity of 66% for CT. A meta-analysis of 18 studies demonstrated an overall sensitivity of 84% and specificity of 89%. Toloza and associates also showed that combining CT and PET resulted in the highest diagnostic accuracy, with a sensitivity of 94% and a specificity of 86%, supporting the use of both modalities for staging of the mediastinum. PET also resulted in a stage different from the one arrived at by the standard methods in 62 of 102 patients, correctly indicating a lower stage in 20 patients and a higher stage of disease in 42 patients. PET was effective in identifying occult metastatic disease. In 11 patients (11%), PET demonstrated distant metastatic disease in bone, liver, and adrenal glands not detected by CT.

During the past decade, integrated PET-CT scanners have replaced PET alone, leading to improved diagnostic accuracy and anatomic localization of disease. Cerfolio and coauthors compared PET with and without integrated CT in 129 patients with biopsy-proved or suspected NSCLC who subsequently underwent surgical staging. PET-CT was a significantly better predictor of stages I and II disease and demonstrated superior accuracy for both T status (70% versus 47%, P = 0.001) and N status (78% versus 56%, P = 0.008) compared with

**Positron Emission Tomography**

Whole-body positron emission tomography (PET) is a physiologic imaging technique based on the detection of positrons emitted by low-atomic-weight isotopes (carbon, fluorine, oxygen, nitrogen). Fluorodeoxyglucose (FDG) labeled with radioactive fluoride (\(^{18}\)F) is a D-glucose analog that is phosphorylated after cellular uptake and accumulates intracellularly, rather than being metabolized. Because lung cancer cells have an increased rate of glycolysis and overexpress the glucose transporter, there is preferential accumulation and visualization of FDG in the primary tumor and in potentially metastatic sites. The criterion for an abnormal PET scan is either a standardized uptake value (SUV) of greater than 2.5 or uptake in the lesion that is greater than the background activity of the mediastinum. The lower limit of resolution of PET is approximately 1.0 to 1.2 cm and thus PET may not detect very small malignant lesions. Benign inflammatory or infectious conditions (e.g., granulomas, sarcoidosis) can also produce false-positive PET findings.
PET alone. Moreover, PET-CT was more sensitive and more specific and had a higher positive predictive value for the status of N1 and N2 disease (\(P < 0.05\)). As in prior studies, PET-CT identified 19 (14.7\%) patients with M1 disease.

PET-CT has proved to be more accurate than a bone scan, with a similar sensitivity and a higher specificity.\(^3\) In the largest study comparing PET with bone scan, Song and colleagues retrospectively analyzed 1000 newly diagnosed patients, 105 of whom were eventually diagnosed with bone metastases and underwent PET-CT and bone scan.\(^3\) PET-CT was more accurate (98.3\% versus 95.1\%, \(P < 0.001\)), sensitive (94.3\% versus 78.1\%, \(P = 0.001\)), and specific (98.8\% versus 97.4\%, \(P = 0.006\)) than bone scan. PET-CT also showed a lower incidence of false positives (1.2\% versus 2.9\%) and false-negative results (5.7\% versus 21.9\%) compared with a bone scan. Agreement between PET-CT and bone scan findings was good, with a calculated \(k = 0.732\). Based on its clear advantages in both intra- and extrathoracic staging, PET-CT is now a routine part of pretreatment staging.

### Bone Scan

Although PET-CT has essentially replaced bone scans for evaluation of potential skeletal metastases, when used in the setting of a positive clinical assessment (e.g., bone pain or tenderness), a technetium-99m methylene diphosphonate (99mTc MDP) whole-body bone scan is relatively sensitive but not specific. In their meta-analysis of seven studies and 633 patients, Toloza and colleagues\(^2\) showed that bone scans have an overall sensitivity of 87\% and specificity of 67\%. False-positive abnormalities are more common when scans are done in asymptomatic patients and can be the result of degenerative or traumatic skeletal injury. Follow-up with magnetic resonance imaging may or may not aid in establishing a definitive diagnosis. False-negative results, although uncommon, do occur, and in one series 6\% of patients with an initially negative bone scan developed confirmed skeletal metastases within 1 year.\(^3\)

### Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the chest offers few advantages over CT in the diagnosis or staging of lung cancer. Heelan and coworkers\(^4\) evaluated both CT and MRI in otherwise operable patients with NSCLC and found that MRI was no more accurate than CT in identifying hilar or mediastinal lymph node metastases and actually had a higher false-positive rate. In a recent study, whole-body MRI with diffusion-weighted imaging was compared with FDG-PET-CT in 33 patients before surgery for lung cancer. Whole-body MRI had comparable sensitivity, specificity, and accuracy for tumor detection and staging but showed no superiority to PET-CT.\(^5\) However, MRI can be useful in some situations. When tumors are adjacent to the spine, MRI provides superior visualization of the spinal canal and can more accurately detect subtle changes in the marrow suggestive of invasion. It also delineates the relationship of a superior sulcus carcinoma (Pancoast tumor) to the subclavian vessels and brachial plexus more accurately than CT.

### Invasive Modalities

#### Bronchoscopy

Rigid or flexible bronchoscopy with conventional white light allows visualization of the tracheobronchial tree and is a standard part of evaluating patients with known or suspected lung cancer. It serves several critical purposes: diagnosis, staging, assessment of resectability, and visualization of the remaining bronchial tree. Flexible video-assisted bronchoscopy has replaced rigid bronchoscopy for all but a few special circumstances. It is generally performed as an outpatient procedure on a spontaneously breathing patient through the nasal or oral route, following topical anesthesia and sedation. The tracheobronchial tree up to the second or third subsegmental bronchi is easily visualized. The options available to secure a diagnosis include direct biopsy, brushing, saline lavage for cytology, and transbronchial needle aspiration (TBNA) with or without fluoroscopic guidance. Using more than one technique (e.g., biopsy, brushing, and cytologic lavage) generally improves the diagnostic yield.

When bronchoscopy reveals an endobronchial tumor, biopsy is best accomplished with either a forceps or brush biopsy, with sensitivities in the range of 80\% to 100\%.\(^6,7\) Positive endobronchial findings are common in cases of squamous and small cell cancers because of their central location. In contrast, a bronchoscopic examination is likely to yield normal findings when there are peripheral lesions, and the diagnostic sensitivity of bronchoscopy varies widely from 37\% to 98\%, depending on the size and location of the target lesion. Increasing size and presence of a bronchus sign (a bronchus leading to or contained in a lesion on CT) portend a higher diagnostic yield.\(^7\) The use of fluoroscopy to guide a transbronchial biopsy or TBNA and lavage can improve diagnostic accuracy up to 80\%.\(^8\) Electromagnetic navigation bronchoscopy (ENB) is a new technology that uses high-resolution CT to guide transbronchial biopsy in real time during bronchoscopy. The CT-based “navigation” of the bronchoscope allows accurate biopsy of small peripheral lung lesions, especially when coupled with rapid on-site cytologic evaluation.\(^9\)

TBNA can also be used when there is bronchial distortion (thickening or blunting of the carina, extrinsic compression) secondary to the lesion or metastatic lymph nodes. Popularized by Wang and Terry, TBNA is performed with a 20- to 22-gauge, rigid needle through the channel of the fiberoptic bronchoscope to puncture the airway in the area of interest.\(^10\) It is a safe and inexpensive procedure with an overall sensitivity of 50\% and a specificity of 96\%.\(^1,6,7\) As previously mentioned, diagnostic yield is enhanced by the use of fluoroscopy, as well as the use of rapid, on-site cytopathology. A positive result, especially from a mediastinal lymph node station, can obviate further surgical staging, although a negative result should still be confirmed surgically. Limitations include a sensitivity of only 30\% for small (<2 cm),
Peripheral lesions and inaccessibility of certain lymph node stations, including anterior, aortopulmonary, paraesophageal, and pulmonary ligament nodes. This technique has now been largely supplanted by the more recent development of endobronchial ultrasound.

Endobronchial Ultrasound

In an effort to improve the diagnostic accuracy of TBNA, endobronchial ultrasound (EBUS) was developed and commercially introduced in the early 1990s. The original probe was radial, and radial EBUS guidance was shown to improve the yield of TBNA in the lymph node staging of lung cancer. Subsequently, an ultrasonic endoscope with a built-in linear-array, convex probe at the tip was developed by the Olympus Corporation (Tokyo) to enable real-time EBUS-guided TBNA. This EBUS is integrated with a convex transducer at 7.5 MHz at the tip of a flexible bronchoscope (XBF-UC260F-OL8, Olympus), whose angle of view is 90 degrees and direction of view is 30 degrees forward oblique. The ultrasound scans parallel to the insertion direction of the scope, and images are obtained by directly contacting the probe, with or without a saline-filled balloon at the tip. The ultrasound image is processed by a dedicated scanner (EU-C2000) that allows for image freezing, size measurement, and Doppler mode. A special 22-gauge needle is passed under direct visualization through the instrument channel to biopsy the target lesion through the bronchial wall (Fig. 16-3). The procedure can be done under monitored anesthesia care or general anesthesia. Indications for EBUS-TBNA include diagnosis of lung and mediastinal tumors and assessment of mediastinal and hilar lymph nodes. Accessible nodal stations include levels 2, 3, 4, 7, 10, and 11. Subaortic, paraesophageal, peribronchial, segmental, and subsegmental nodes are generally not approachable. Several studies have shown the accuracy of EBUS-TBNA for mediastinal and hilar nodal staging in NSCLC. In one of the earliest series, Yasufuku and colleagues successfully performed EBUS-TBNA in 105 patients with proved or suspected lung cancer and adenopathy by CT criteria alone. They sampled 163 lymph nodes and reported an overall diagnostic accuracy rate of 96.3%, with a sensitivity of 94.6% and a specificity of 100%. Of note, patients who proved to have benign disease were excluded from analysis, and not all patients had confirmatory surgical biopsy of the nodal stations biopsied by EBUS. In a subsequent prospective controlled trial, Yasufuku and colleagues performed EBUS-TBNA followed immediately by cervical mediastinoscopy, in 153 patients with known or suspected lung cancer. No significant differences were found between EBUS-TBNA and mediastinoscopy with respect to sensitivity, negative predictive value, diagnostic accuracy, and determination of true pathologic N stage. The same group of investigators has also reported that EBUS-TBNA can accurately access hilar and interlobar lymph nodes. The accuracy of EBUS-TBNA is enhanced by rapid on-site evaluation (ROSE) of cytology specimens during the procedure, which also optimizes specimen submission for tumor molecular profiling. A recent meta-analysis of 1066 patients from nine studies confirms the excellent accuracy of EBUS-TBNA. In many centers, EBUS-TBNA has largely replaced mediastinoscopy in the staging of resectable NSCLC.

Autofluorescence Bronchoscopy

Detection and treatment of dysplastic or early invasive centrally located neoplastic lesions whose presence is suggested by positive sputum cytology remain a challenge. Approximately one third of patients with positive sputum cytology, but radiographically occult lung cancers, require more than one bronchoscopy for localization. In an effort to improve identification of superficial bronchial mucosal malignancy, Hung and associates were able to demonstrate that normal and malignant bronchial mucosa have different autofluorescence intensities under blue light (wavelength, 442 nm). This led to the development of the LIFE (light imaging fluorescence endoscope) Lung system (Xillix Technologies, Richmond, BC, Canada). Whereas normal bronchial mucosa appears green, premalignant and malignant tissue appears brown-red. Subsequent prospective trials comparing white-light bronchoscopy with white-light bronchoscopy

![Figure 16-3](image-url) **Figure 16-3** A, CT scan of the chest revealing enlarged right paratracheal lymph node. B, Endobronchial ultrasound (EBUS)-guided transbronchial needle aspirate of an enlarged right paratracheal lymph node.
plus LIFE have shown enhanced sensitivity in detection of intraepithelial neoplasms and invasive carcinoma. Lam and coworkers reported the results of a multicenter North American trial of 173 patients that showed the relative sensitivity of white-light bronchoscopy plus LIFE versus white-light bronchoscopy alone to be 6.3 for intraepithelial lesions and 2.7 if invasive cancers were included. The role of LIFE was in preoperative screening for synchronous squamous carcinomas but in follow-up for recurrence or second primary tumors, and for monitoring intraepithelial dysplasia in some chemoprevention trials, it is not currently in widespread use. This relates in part to the epidemiologic shift away from centrally located squamous cancers and in part to the lack of development of more advanced autofluorescence technology than can be used outside of the research setting.

**Percutaneous Transthoracic Needle Biopsy**

Percutaneous transthoracic needle biopsy is a well-established procedure used to obtain a tissue diagnosis of lung cancer in patients who are not surgical candidates because of advanced disease or medical contraindications. However, with the identification of increasing numbers of noncalcified peripherally located pulmonary nodules by low-dose CT, transthoracic needle biopsy has become a critical tool in the detection of early-stage lung cancer. The accuracy of percutaneous needle biopsies has been enhanced by the development of fluoroscopy CT, which allows precise targeting of very small peripheral nodules for biopsy. The most common complications of the procedure are pneumothorax and mild hemoptysis. Although the reported incidence of pneumothorax varies greatly, the rate of postprocedure pneumothoraces requiring intervention ranges from 1.6% to 17%. The most important risk factor is underlying chronic obstructive pulmonary disease (COPD). Hemoptysis occurs in 5% to 10% of cases and is usually self-limited. Massive hemoptysis is rare with the use of 20-gauge or smaller needles. Relative contraindications to transthoracic biopsy, therefore, are the presence of severe COPD, a bleeding disorder, contralateral pneumectomy, and severe pulmonary hypertension. When successful, the results of percutaneous transthoracic biopsy are positive in patients with lung cancer in roughly 90% of cases, with a low false-positive rate of less than 2%. However, false-negative results can be frequent, so all results should be considered indeterminate unless a specific benign diagnosis is made.

**Cervical Mediastinoscopy**

Accurate assessment of the mediastinum is paramount as mediastinal lymph node involvement by metastatic carcinoma strongly influences treatment decisions. Until the development of EBUS, cervical mediastinoscopy was the most accurate pre-resection method of staging the mediastinum in lung cancer. Described by Carlens in 1959, mediastinoscopy is performed with a rigid, lighted scope placed in the avascular, pretracheal space to access the superior mediastinum. Its efficacy is well established, with a pooled procedural sensitivity of 81% and a specificity of 100% in a recent meta-analysis of 5687 patients. A negative mediastinoscopy also predicts a high rate of complete resection at thoracotomy. Lam and colleagues demonstrated that of 590 patients with a negative mediastinoscopy, 93% had complete tumor resection. Cervical mediastinoscopy is an outpatient procedure that is extremely safe. In a review of 2137 patients, Hammond and coworkers reported overall morbidity and mortality rates of 0.6% and 0.05%, respectively.

In the pre-EBUS era, the indications for mediastinoscopy were often debated and routine mediastinoscopy was controversial. Most thoracic surgeons agreed that mediastinoscopy should be performed for the following: (1) lymph node enlargement greater than 1 cm in the short axis on CT, (2) hypermetabolic uptake on PET, and (3) possible enrollment into induction therapy protocols. Relative indications included the presence of T2 or T3 tumor or poor prognostic tumor histologies such as large cell carcinoma. Those who supported the practice of routine mediastinoscopy emphasized its low complication rate and high level of accuracy, the high rate of complete resection after a negative mediastinoscopy, the relatively low sensitivity of CT, the prevalence of nodal disease even in T1 tumors (Table 16-3), and the ability to select patients who might benefit from induction therapy. During the past decade, the combination of PET-CT and EBUS-TBNA has gradually replaced mediastinoscopy in the staging of NSCLC. However, mediastinoscopy remains appropriate in situations where EBUS-TBNA samples are inadequate for diagnosis or for tumor molecular profiling.

**Left Anterior Mediastinotomy and Extended Cervical Mediastinoscopy**

One limitation of mediastinoscopy can be in the setting of a left upper lobe cancer, in which aortopulmonary window and para-aortic lymph nodes (levels 5 and 6) may

<table>
<thead>
<tr>
<th>TABLE 16-3 Prevalence of Nodal Metastases in Clinical T1 Non–Small Cell Lung Cancer</th>
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</thead>
<tbody>
<tr>
<td>Author (ref)</td>
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<tr>
<td>-------------</td>
</tr>
<tr>
<td>Ishida et al</td>
</tr>
<tr>
<td>Naruke et al</td>
</tr>
<tr>
<td>Asamura et al</td>
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<tr>
<td>Oda et al</td>
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<td>Graham et al</td>
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ISBN: 978-0-323-24126-7; PII: B978-0-323-24126-7.00016-8; Author: Sellke & del Nido & Swanson; 00016
need to be sampled. In this situation, there are two options for surgical staging. Levels 5 and 6 mediastinal lymph nodes can be accessed from a left anterior or para-sternal approach, as described by McNeill and Chamberlain.46 A transverse incision is placed over the second rib, and the costal cartilage is removed. The retrosternal extrapleural space is entered by blunt dissection, and the para-aortic space is explored. Modifications of the procedure include preservation of the internal mammary vessels, use of the mediastinoscope for better visualization, and preservation of the cartilaginous rib. In three reported series totaling 194 patients with left upper lobe cancers who underwent a Chamberlain procedure, 38% (73 of 194) had positive biopsy results, and resectability in those patients with a negative anterior mediastinotomy was 95%.76 As with cervical mediastinoscopy, morbidity and mortality rates in previously reported series are low—8% and 0%, respectively.

Another surgical approach to the anterior mediastinum in left upper lobe cancers is extended mediastinoscopy, described by Ginsberg and associates.77 After a pathologically negative standard cervical mediastinoscopy, the mediastinoscope is withdrawn, and blunt digital dissection is used to create a window between the innominate and left carotid arteries posterior to the innominate vein. The mediastinoscope is reinserted and advanced along the anterolateral surface of the aortic arch into the node-containing fat pad. Extended mediastinoscopy should be avoided in patients with a dilated or calcified aortic arch or previous sternotomy. Because of the challenging nature of the dissection required for extended mediastinoscopy and the development of other minimally invasive alternatives to accessing the aortopulmonary window, such as EUS and video-assisted thoracic surgery, extended mediastinoscopy is no longer widely performed.

Scalene Node Biopsy

Scalene node biopsy is used to assess suspect nodes in the supracavicular fossa, identified by either palpation or imaging (specifically, PET-CT). If there are palpable nodes in the supracavicular fossa, a fine-needle aspiration (FNA) in the office is often sufficient. If an FNA is nondiagnostic, or metastatic disease is suspected on imaging, formal excision of the fat pad may be performed. A 3- to 4-cm incision is placed over the insertion of the sternocleidomastoid muscle parallel to the clavicle. Dissection is performed between the clavicular and sternal heads, exposing the scalene fat pad on top of the scalene anterior muscle. Care must be taken to preserve the phrenic nerve lying posterior on the scalene anterior muscle. Scalene node biopsy can also be done during a mediastinoscopy using a single incision. Lee and Ginsberg reported that 15.4% of patients (6 of 39) with positive N2 disease had positive scalene nodes as well, indicating N3 disease.77

Video-Assisted Thoracic Surgery

Video-assisted thoracic surgery (VATS), now performed with a videothoracoscope, is a valuable tool for the diagnosis and staging of NSCLC. It requires general anesthesia and a patient who can tolerate single-lung ventilation. With the patient in a standard lateral decubitus position, the thoracoscope and endoscopic instruments are inserted through one or more operating ports placed via small intercostal incisions. The entire hemithorax can be explored, including the hilum, mediastinum, visceral and parietal pleural surfaces, and chest wall. The principal use of VATS has been to perform the excisional biopsy of peripheral lung nodules for the diagnosis of primary lung cancer or to rule out synchronous or metastatic disease.71 It can be used to evaluate mediastinal lymph nodes—in particular, those inaccessible by cervical mediastinoscopy (anterior, aortopulmonary, para-aortic) or anterior mediastinotomy (hilar, inferior pulmonary ligament).74,75 Several studies have shown that the sensitivity and accuracy of VATS are almost 100% for diagnosis and staging of lung cancer, with minimal morbidity and mortality.

Thoracotomy

With the myriad of accurate, less invasive diagnostic methods available, more than 95% of tumors can be characterized without thoracotomy. Exploratory thoracotomy, however, still allows the most thorough assessment of the primary lesion, the pleural space, and the ipsilateral mediastinal lymph nodes. The tumor is typically biopsied with a Tru-Cut needle, and the local extent and status of the mediastinal lymph nodes are assessed while the pathologists analyze the specimen by frozen section.

METASTATIC WORKUP

Approximately 40% of patients with newly diagnosed lung cancer are found to have extrathoracic metastases. Identifying these patients is critical to avoid unnecessary thoracotomy and a delay in appropriate systemic therapy. Currently, the standard multiorgan imaging techniques used to rule out the most common metastases in patients with NSCLC (adrenal, liver, brain, bone) are CT of the chest and upper abdomen, CT or MRI of the brain with contrast, and whole-body PET-CT. Who should undergo evaluation for distant metastatic disease? There are few prospective randomized trials of extrathoracic imaging for NSCLC. It is well accepted that patients who have certain symptoms, abnormal physical findings, or laboratory abnormalities are at increased risk of having metastatic disease. Silvestri and coauthors showed in a large meta-analysis that a positive clinical evaluation was associated with a roughly 50% rate of abnormal scans.78 These results underscore how critical the findings of the initial history, physical examination, and laboratory tests are in guiding subsequent workup. Patients with a positive clinical evaluation (Table 16–4) should undergo multiorgan scanning. What about asymptomatic patients? Routine multiorgan imaging in patients without symptoms or signs is controversial. Several studies have shown that routine preoperative scanning in asymptomatic patients is
TABLE 16-4 Clinical Evaluation for Metastatic Disease

<table>
<thead>
<tr>
<th>Clinical Evaluation</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Constitutional: weight loss &gt;5% of body weight, malaise</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal: focal skeletal pain</td>
</tr>
<tr>
<td></td>
<td>Neurologic: headache, seizure, mental status or personality changes</td>
</tr>
<tr>
<td>Physical signs</td>
<td>Focal neurologic deficit</td>
</tr>
<tr>
<td></td>
<td>Supraclavicular lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Hoarseness</td>
</tr>
<tr>
<td></td>
<td>Superior vena cava syndrome</td>
</tr>
<tr>
<td></td>
<td>Bony tenderness</td>
</tr>
<tr>
<td></td>
<td>Skin or soft tissue mass</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td></td>
<td>Elevated liver function tests</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
</tr>
</tbody>
</table>

Associated with a low percentage (3% to 10%) of positive results, with silent metastases found in 2.7% to 15%. In their meta-analysis, Silvestri and colleagues calculated the probability that a scan will be negative if the clinical evaluation is negative (i.e., the negative predictive value of the clinical evaluation). For CT of the abdomen or brain, and for bone scan, the negative predictive values were 94%, 95%, and 89%, respectively. The only prospective, randomized trial that compared routine multiorgan scanning with chest CT and mediastinoscopy in asymptomatic patients with clinically operable lung cancer showed no statistically significant difference in the rate of unnecessary thoracotomy, postoperative recurrence, or overall survival. Despite this, more recent data have shown whole-body PET and PET-CT to be invaluable in disclosing non–central nervous system metastatic disease in up to 10% to 20% of cases missed by standard methods. On this basis, PET-CT should be considered a standard staging modality in all cases of biopsy-proven or suspected lung cancer, and it obviates the need for bone scan as well.

In addition, some authors have reported that more locally advanced lesions (T3 or N2) have a higher rate of asymptomatic distant metastases. Others have shown that adenocarcinomas have a higher rate of asymptomatic cerebral metastases than squamous carcinomas. However, the evidence to support routine brain imaging in the evaluation of potentially resectable NSCLC is scant and is based primarily on retrospective series. MRI with or without intravenous gadolinium is considered the optimal imaging study. A generally accepted approach is to add brain MRI to CT and PET-CT for evaluation of clinically higher stage tumors (stages II and III) but not for stage I tumors where the frequency of asymptomatic brain metastases is only about 5%. Based on available information, it is appropriate for all patients with established or suspected lung cancer to undergo high-resolution, contrast CT of the chest and whole-body PET-CT. Selected patients should undergo brain MRI. Multigorgan scanning should be considered for (1) any patient with a positive clinical evaluation (symptoms, signs, blood work), (2) patients with locally advanced disease (stage IIIA) being considered for multimodality therapy, and (3) patients with earlier stage disease (stages I, II) who are marginal operative candidates.

SUMMARY

Lung cancer remains a challenging and deadly disease. Proper diagnosis and staging are critical for determining the best treatment strategy for each patient. The most important components of the workup are the initial history and the physical examination. Numerous noninvasive and invasive techniques can be used to establish an accurate and valid clinical estimate of tumor stage.

REFERENCES


ISBN: 978-0-323-24126-7; PII: B978-0-323-24126-7.00016-8; Author: Sellke & del Nido & Swanson; 00016


SECTION 1  THORACIC SURGERY


