Clinical Evaluation and Staging of Patients Who Have Lung Cancer

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The diagnostic and staging evaluation of a patient who is suspected of having lung cancer can be complex and time consuming [1]. Several diagnostic and staging tests may be considered in this evaluation. An understanding of the characteristics of a test, as well as the clinical situations in which it has been shown to be most accurate is important to minimize the chance of misinterpreting a positive or negative result. For example, positron emission tomography (PET) is being used increasingly in the diagnosis and staging of a patient who is suspected of having lung cancer [2,3]. The accuracy of this test has been established most for patients who have non-small cell lung cancer (NSCLC); there is less experience in patients who have small cell disease. PET is particularly accurate in the evaluation of a primary tumor and in the evaluation of extrathoracic metastases [2–4]. In contrast, PET is less accurate in staging mediastinal lymph nodes; its role in this setting is being questioned increasingly [3,5].

The clinical evaluation remains the most important starting point in the work-up of a patient who is suspected of having lung cancer. The initial symptoms, as well as chest imaging, often can be used to establish a presumptive diagnosis and stage. This information can be used to guide further testing. The staging algorithm for NSCLC and small cell lung cancer (SCLC) should proceed in a sequential fashion with the goal of identifying patients who can be treated with curative intent as quickly and efficiently as possible, while minimizing expensive and invasive testing [6,7]. This evaluation also needs to identify patients who...
have incurable disease accurately to minimize the risk of exposing these patients to the morbidity of surgery or combined-modality approaches. This article updates the performance characteristics of the most commonly used diagnostic and staging modalities in the evaluation of a patient who has lung cancer. Recent data with newer modalities, like PET, also are reviewed and their role in this evaluation are discussed.

Clinical presentation

Most patients who have lung cancer present with symptoms that are related to the primary tumor or intrathoracic spread of disease (cough, hemoptysis, dyspnea, chest pain, hoarseness, wheezing), distant metastatic disease, or nonspecific systemic symptoms (fatigue, weight loss, generalized weakness) [8–10]. Less than 10% of patients are asymptomatic at presentation [9,10]. In a population-based series of patients from New Hampshire and Vermont, the most common symptoms at presentation included weight loss (46%), cough (45%), dyspnea (37%), weakness (34%), chest pain (27%), and hemoptysis (27%) [8]. This is consistent with data reported from other series [9,11]. Although the frequency of hemoptysis was higher for patients who had squamous cell tumors, there was little correlation between cell type (small cell versus non–small cell) and clinical presentation [8].

Radiographic findings based on cell type

A chest radiograph (CXR) commonly is the first step in the evaluation of a patient who is suspected of having lung cancer. Quinn and colleagues [12] published the CXR findings from 345 consecutive cases of lung cancer that were recorded in a tumor registry in Wisconsin from 1990 to 1992. Adenocarcinoma was the most common cell type, followed by squamous cell, small cell, and large cell carcinoma (Table 1). Overall, peripheral and central masses were seen in 43%

<table>
<thead>
<tr>
<th></th>
<th>Incidence (%)</th>
<th>Peripheral</th>
<th>Central</th>
<th>Obstruction</th>
<th>Pleural effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>36</td>
<td>49</td>
<td>49</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>28</td>
<td>43</td>
<td>61</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>Small cell</td>
<td>25</td>
<td>37</td>
<td>77</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Large cell</td>
<td>6</td>
<td>15</td>
<td>41</td>
<td>27</td>
<td>14</td>
</tr>
</tbody>
</table>

and 52% of cases, respectively. Pleural effusions were seen in 20% of cases and there was no difference in the incidence of pleural effusions based on cell type.

Adenocarcinoma represents approximately 20% to 40% of lung cancers [12,13]. Although it commonly is believed to present as a peripheral lung mass, the incidence of peripheral and central adenocarcinomas was equivalent (49%) in the Wisconsin series [12]. When occurring peripherally, the incidence of hilar and mediastinal adenopathy was 18% and 2%, respectively [14]. In contrast, metastatic disease to hilar and mediastinal lymph nodes occurs more commonly with central adenocarcinomas (40% and 27%, hilar and mediastinal lymph nodes, respectively) [14].

Bronchioloalveolar cell carcinoma (BAC) is a unique subtype of adenocarcinoma that may have a different etiology and can have a varied clinical and radiographic presentation [14,15]. Approximately 2% to 37% of all cases of lung cancer are BAC [15]. A peripheral solitary pulmonary nodule is the most common CXR finding [15]; however, other common radiographic presentations include multiple pulmonary nodules and focal or multiple bilateral scattered opacities [14–16]. Approximately 60% of cases present as a solitary nodule or localized infiltrate, 23% present as diffuse or bilateral disease, and 11% present as multifocal nodules [15]. Hilar and mediastinal adenopathy are uncommon findings at presentation and occur in less than 20% of cases [14].

The prevalence of squamous cell carcinoma has been decreasing in recent series; it accounts for 4% to 25% of lung cancers [12,13]. Most are found within central bronchi; only one third occur beyond the segmental bronchi [14]. Cavitation and segmental or lobar lung collapse are common radiographic findings [14]. The prevalence of large cell carcinoma also is low and accounts for less than 10% of lung cancers [16]. Most patients who have large cell carcinoma have peripheral tumors on chest imaging, which have been characterized by rapid growth with early development of local and distant metastases [16].

Approximately 15% to 20% of lung cancers have small cell histology [14,16]. The most common radiographic findings include central tumors with mediastinal extension and hilar and mediastinal adenopathy. Overall, 70% to 80% of patients have a mass within or near the hilum [17–19]. Peripheral tumors are less common and frequently are associated with hilar adenopathy [14]. Like large cell carcinoma, small cell disease frequently disseminates early in its natural history; most patients present with clinical or radiographic evidence for distant metastatic disease.

Diagnosing the primary tumor

Clinical assessment

A solitary lung lesion that is less than 3 cm in size commonly is referred to as a nodule, whereas a lesion that is greater than 3 cm is referred to as a mass [20]. Overall, between 15% and 75% of solitary pulmonary nodules (SPNs) prove to
be malignant, depending on the population that is studied [20–22]. In a recent series of 360 patients from a university-affiliated Veterans Administration Medical Center, the proportion of resected SPNs that was malignant increased over time, from 55% to 60% in 1981 to 1983 to 90% to 100% in 1990 to 1994 ($P<.005$) [21]. The investigators suggested that this trend reflected an improved ability to diagnose an SPN more accurately with CT imaging.

Several reviews have summarized the radiographic characteristics that can help to differentiate between a benign and a malignant SPN [14,16,20,23]. The two most common radiographic characteristics on a CXR that suggest a benign lesion include a “benign” calcification pattern and the lack of growth over a 2-year period of time [14,20,23,24]. Benign calcification patterns that are seen on CXR include diffuse, concentric laminar, dense central, and a “popcorn” pattern [14,20,23,25]. The first three characteristics are associated commonly with granulomatous disease, whereas the last has been described with hamartomas. Calcification can be seen in malignant lesions—most commonly in an eccentric pattern, but occasionally in a stippled pattern [23,25]. Other potentially helpful characteristics that may raise the likelihood of a benign process include rapid (<7 days) or slow (>465 days) doubling time, a fat density or smooth border on CT imaging, and small size (<2 cm) [20,23]. Most SPNs that are greater than 2 cm in size are malignant [20,23,26]. Radiographic characteristics that are more suggestive of a malignant process include ill-defined margins, irregular and spiculated borders, cavitation, and upper lobe location [23,24,27].

There have been multiple attempts to quantify the risk that a given SPN will have malignant cells through the development of mathematical models that incorporate available clinical and radiographic factors [28–30]. Swensen and colleagues [29] developed a clinical prediction model from 8 clinical and 11 radiographic factors in 419 patients who had SPNs that ranged in size from 4 mm to 30 mm. In a multivariate logistic regression analysis, significant independent predictors of a malignant SPN included advanced age, cigarette smoking, history of extrathoracic disease, SPN diameter, spiculation, and upper lobe location. The same investigators compared the clinical prediction model with the predictions of malignant involvement of similar-sized SPNs that were made by four physicians, including a general internist, a pulmonologist, a thoracic surgeon and a chest radiologist [31]. In this comparison, there was no significant difference in the ability to predict a malignant SPN between the two groups.

PET scanning has been used increasingly as a diagnostic tool in the evaluation of focal pulmonary lesions [4,32,33]. The average sensitivity of PET imaging to detect primary lung cancer was reported to be 97%, with a specificity of 78% and false negative and false positive rates of 8% and 10%, respectively [23]. This is consistent with data from a meta-analysis that was reported by Gould and colleagues [4]. In this analysis, there was no difference in the diagnostic accuracy of PET imaging for pulmonary nodules based on size ($P = .43$) [4]; however, most studies included patients who had pulmonary nodules that were greater than 1.0 cm. False negative rates for lesions that are up to 1.5 cm were reported to be as high as 18% [32]. Likewise, false negative PET results have been reported for
nodules from BAC and carcinoid tumors [34–36]. Consequently, PET imaging generally is not recommended for nodules that are less than 1.0 cm or if BAC or carcinoid is suspected based on the clinical presentation. False positive results have been reported in infectious (tuberculosis and histoplasmosis) and inflammatory (rheumatoid nodules) conditions [34,37]. Therefore, a positive result should be confirmed with a tissue diagnosis.

The decision to use PET in the evaluation of an SPN or lung mass depends on an assessment of the likelihood that the lesion is a lung cancer. Based on the clinical and radiographic presentation, if a lesion (>1.0 cm) is believed to have a low to intermediate likelihood for being a lung cancer (5%–80%), then a PET scan may provide useful information [2,4,33]. Based on the meta-analysis, if a lesion has a 20% likelihood of being malignant, the posttest probability is approximately 1% if the test is negative [4]. In this setting, observation with follow-up imaging would be reasonable [2]. If a patient has a high (>80%) likelihood of having a lung cancer, PET imaging is far less useful [2,4]. The posttest probability of malignancy after a negative PET scan would still be approximately 14% [4].

Establishing a tissue diagnosis

The decision to pursue a tissue diagnosis of the primary tumor depends on the initial clinical impression of the lesion, including the likelihood that it represents a primary lung cancer and an initial assessment of the cell type (small cell versus non–small cell). If small cell disease is believed to be likely, a tissue diagnosis should be obtained in whatever manner is easiest for the patient [19]. If the likelihood of malignancy is considered to be high, a tissue diagnosis can be confirmed at the time of the definitive anatomic resection. For lesions with an intermediate or lower likelihood of malignancy, a tissue diagnosis can be pursued best with sputum cytology or bronchoscopy if the lesion is located centrally, and a transthoracic needle aspiration (TTNA) if the lesion is peripheral [38].

In 2003, the Duke University Center for Clinical Health Policy Research performed a comprehensive review of the published literature and summarized the performance characteristics of these modalities (Table 2) [38]. The average sensitivity and specificity of sputum cytology were 66% and 99%, respectively.

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FP</th>
<th>FN</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum cytology</td>
<td>28,477</td>
<td>0.66</td>
<td>0.99</td>
<td>0.09</td>
<td>0.06</td>
<td>0.15</td>
</tr>
<tr>
<td>Bronchoscopy—central tumors</td>
<td>3754</td>
<td>0.88</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bronchoscopy—Peripheral tumors</td>
<td>4136</td>
<td>0.69</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Transthoracic needle biopsy</td>
<td>12,207</td>
<td>0.90</td>
<td>0.97</td>
<td>0.02</td>
<td>0.29</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Abbreviations: FN, false negative rate; FP, false positive rate; NR, not reported.

The accuracy of this technique is dependent on the number of specimens that are analyzed, preservation techniques, and size and location of the tumor [19,38]. The average sensitivity of sputum cytology for peripheral tumors was only 49% [38]. The overall sensitivity of flexible bronchoscopy for central tumors in this analysis was 88%, compared with 69% for peripheral tumors [38]. Of the techniques that were used in conjunction with flexible bronchoscopy, endobronchial biopsies were associated with the highest sensitivity (74%), followed by brushings (59%) and washings (48%). The sensitivity for peripheral lesions was greater for tumors that were larger than 2 cm (62%) than for those that were smaller than 2 cm (33%) [38].

Lacasse and colleagues [39] conducted a meta-analysis of the accuracy of TTNA. Forty-eight studies were identified; the pooled sensitivity for differentiating between a malignant process versus all other categories was 86.1% (range 83.8%–88.45%) with a specificity of 98.8% (98.4%–99.2%). This analysis was updated by the Duke University Center for Health Policy Research with the inclusion of 19 additional studies [38]. In addition, 5 studies that initially were included in the Lacasse et al analysis were excluded in this update because of small sample size (<50 patients). The overall pooled sensitivity was 90% (range 62%–99%), with a specificity of 97% (range 93%–100%) [38]. There was little difference in the sensitivity based on tumor size (95% and 91%, >2 cm and <2 cm, respectively). Pneumothorax represents the main complication of a TTNA. In the Lacasse et al analysis, the overall pooled incidence rate of pneumothorax was 24.5% (range 3.1%–41.7%), with a 6.8% (range 0%–16.6%) rate of chest tube placement [39].

In general, a positive result from sputum cytology, bronchoscopy, or TTNA is considered to be reliable because false-positive results typically have been reported to be less than 2% for all three studies [23,38,39]. Likewise, the ability to differentiate between small cell and non–small cell histology is considered high. In the Duke analysis, the overall accuracy in differentiating between non–small cell and small cell disease was 98% [38]. The error rate for the diagnosis of small cell histology was slightly higher (9%) compared with the diagnosis of non–small cell histology (2%). Although these diagnostic modalities are useful in confirming the diagnosis, the false-negative rate for all three has not been well-defined, or remains too high to rule out the diagnosis effectively. Therefore, if the clinical suspicion for a lung cancer diagnosis remains high, additional evaluation usually is required after a negative test result.

If a pleural effusion is identified on the initial chest imaging, a diagnostic thoracentesis should be considered; however, the sensitivity of pleural fluid cytology in patients who have a malignant pleural effusion is only approximately 60% [40–43]. The sensitivity increases to 80% if three separate fluid specimens are submitted to an experienced cytologist [42,43]. Pleural fluid cytology is more sensitive than a blind pleural biopsy when diagnosing malignant pleural disease; therefore, this procedure frequently is less helpful when a malignant pleural effusion is suspected [19]. If pleural fluid cytology remains nondiagnostic, a thoracoscopy can be considered for further evaluation. This procedure
is sensitive and specific in the evaluation of a malignant pleural effusion with a high negative predictive value [44,45].

**Staging non–small cell lung cancer**

If the diagnosis of NSCLC is suspected based on the clinical presentation or confirmed by a tissue diagnosis, the TNM system (Table 3) serves as the basis for the staging evaluation [46]. Clinical staging refers to the initial evaluation, including imaging and invasive diagnostic procedures. Pathologic staging is established at the time of resection and is considered to be more accurate. Overall, approximately 40% of patients who have NSCLC present with distant metastatic disease [47]. Another 30% present with locally-advanced disease (stage IIIA/IIIB), and the remaining patients present in either stage I (24%) or stage II (7%).[47]. For most patients, a CXR and subsequent CT scan of the chest serve as the initial testing modalities that allow an assessment of the tumor (T)

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Non–small cell tumor and nodal staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Primary tumor (T)</td>
<td>No evidence for primary tumor</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence for primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>In situ</td>
</tr>
<tr>
<td>T1</td>
<td>≤3 cm, surrounded by lung of visceral pleura, and located no more proximally than lobar bronchus</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;3 cm, or any size with one of the following characteristics: involvement of main bronchus ≥2 cm distal to carina, invasion of visceral pleura, or associated with atelectasis or obstructive pneumonitis extending to hilar region but not including entire lung</td>
</tr>
<tr>
<td>T3</td>
<td>Any tumor size with any of the following characteristics: invasion of chest wall, diaphragm, mediastinal pleura, pericardial pericardium; or tumor in the main bronchus &lt;2 cm from, but not involving, the entire carina; or associated atelectasis or obstructive pneumonitis of the entire lung</td>
</tr>
<tr>
<td>T4</td>
<td>Any tumor size with any of the following characteristics: invasion of the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; or malignant pleural or pericardial effusion; or the presence of a satellite tumor nodule(s) within the same lobe as the primary tumor</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
<td>No lymph node metastasis</td>
</tr>
<tr>
<td>N0</td>
<td>No lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Ipsilateral peribronchial or hilar metastasis, or direct extension to intrapulmonary lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Ipsilateral mediastinal or subcarinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Contralateral mediastinal, hilar or ipsilateral/contralateral scalene, or supraclavicular lymph nodes</td>
</tr>
<tr>
<td>Distant metastasis (M)</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

and nodal (N) status. Routine imaging to evaluate for the presence of extrathoracic metastatic disease in patients who do not have symptoms generally is not recommended. Several factors can be considered when deciding whether to pursue additional imaging studies to evaluate for the presence of distant metastatic disease, including the clinical evaluation, radiographic T and N stage, and histology, if it has been established [48–50]. Of these, the clinical evaluation is the most important factor that should be considered when deciding whether to pursue extrathoracic staging studies.

**Extrathoracic staging**

Silvestri and colleagues [50] performed a meta-analysis of the literature that included studies that were published from 1977 to 1992 that evaluated the performance of the clinical evaluation in the detection of extrathoracic metastases. There were 25 studies included, with a total of 1398 patients. The imaging studies included CT scan of the brain and abdomen, as well as bone scan. The overall median negative predictive value (NPV) of the clinical evaluation was 94% (range 79%–100%). When an expanded clinical evaluation was considered, which included a predefined list of nonspecific indicators to screen for metastatic disease, the overall NPV was higher and ranged between 97% and 100% [50].

The mean positive predictive value (PPV) and NPV of the clinical evaluation in the detection of brain, abdominal (liver or adrenal), or bone metastases were 57% and 94%, 20% and 97%, and 46% and 89%, respectively. An update of this meta-analysis was published and is outlined in Table 4 [51]. Given the low PPV of the clinical evaluation, confirmatory tests should be done in symptomatic patients; these tests should identify metastatic disease in approximately 50% of the patients [50].

Despite the high NPV of the clinical evaluation, selected groups of patients have a higher incidence of occult metastatic disease; routine imaging in these patients may be justified. Although the overall incidence of distant metastases in patients who have clinical stages I or II disease and a negative clinical evaluation is less than 5%, the incidence of occult metastatic disease in patients who have clinical stage III disease was reported to be much higher [3,49]. Using a PET-based staging strategy, MacManus and colleagues [49] reported rates of

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1784</td>
<td>0.76</td>
<td>0.87</td>
<td>0.54</td>
<td>0.94</td>
<td>0.13</td>
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<tr>
<td>Abdomen</td>
<td>1201</td>
<td>0.92</td>
<td>0.49</td>
<td>0.32</td>
<td>0.95</td>
<td>0.10</td>
</tr>
<tr>
<td>Bone</td>
<td>663</td>
<td>0.87</td>
<td>0.67</td>
<td>0.36</td>
<td>0.90</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Abbreviations:* NPV, negative predictive value; PPV, positive predictive value.

asymptomatic metastases in patients who had clinical stages I, II, or III disease to be 8%, 18%, and 24% \( (P = .016) \), respectively. The higher rate of asymptomatic metastases in patients who had stage III disease was reported in other trials [48,52]. In a randomized comparison of CT and MRI imaging of the brain for asymptomatic patients who had operable NSCLC, Yokoi and colleagues [52] reported overall rates of brain metastases in 6% (12/200) of patients who had clinical stages I or II disease and 11% (11/98) of patients who had clinical stages IIIA or IIIB disease. In the updated guidelines from the American Society of Clinical Oncology for the treatment of patients who have unresectable NSCLC, routine PET scan and MRI of the brain is recommended in the extrathoracic staging of patients who have locally-advanced disease who are being considered for surgery or radiation [53].

Of the potential imaging modalities that are available to evaluate for the presence of extrathoracic metastases, PET may be the most accurate [54–56]. The exception is in the evaluation for brain metastases; generally, PET is considered to be less accurate than CT or MRI scanning, with a reported sensitivity of only 60% [54]. In trials that compared PET scanning with traditional imaging (CT scan and bone scan), PET identified additional sites of metastatic disease in approximately 7% to 11% of patients [55,56]. In a series of 100 patients who underwent preoperative staging, PET was 92% sensitive and 99% specific for the identification of bone metastases compared with bone scan, which was 50% sensitive and 92% specific [54]. The increased accuracy of PET for detecting bone metastases was shown in other series as well, with reported false negative and false positive rates of 1% to 2% and 8% to 10%, respectively [57,58]. Likewise, PET was able to characterize adrenal lesions accurately [54]. Compared with reported false positive rates of 60% with CT scans, false positive rates of adrenal imaging were reported to range between 0% and 8% [54,58–60]; however, approximately 60% of patients who present with distant metastatic disease have disease in a solitary site only [58]. Although the false positive rates with PET may be lower than with other imaging studies, a positive result, particularly if only a single abnormality is identified, should be confirmed with a biopsy. In a recent trial that was reported by the American College of Surgeons, an overall false positive rate for the identification of metastatic disease by PET was 7%, with abnormalities noted in several sites that were confirmed subsequently to be benign [61].

**Intrathoracic staging**

The goal of intrathoracic staging is to identify those patients who are most likely to be candidates for surgical resection. This evaluation predominantly focuses on establishing the nodal status, because the presence or absence of N2 or N3 disease have the greatest impact on the decision of whether to pursue surgery. The identification of N1 disease, as well as the differentiation between T1 and T2 tumors have little impact on the surgical decision. Identifying T4 tu-
mors clearly is important; however, this can be difficult to evaluate accurately with CT or MRI imaging of the chest. The average overall sensitivity of the CT scan in differentiating between T3 and T4 tumors is 55%, with a specificity of 89%, and false positive and false negative rates of 32% and 18%, respectively [62]. MRI usually does not provide much additional information in defining the T status with the exception of Pancoast tumors, in which MRI may improve the ability to evaluate the brachial plexus or subclavian vasculature [62].

Table 5 lists the modalities that may be used to define the nodal status. The CT scan is notoriously inaccurate in identifying N2 or N3 disease. Using a cut off of 1 cm, approximately 40% to 45% of enlarged lymph nodes will be benign and 13% to 15% of normal-sized lymph nodes will have occult metastatic disease [51,62–65]. False positive results with CT scans were reported to occur in association with atelectasis, pneumonia, and underlying granulomatous disease and may be more prevalent in patients who have squamous cell carcinomas [66–68]. False negative rates vary and were reported to be as high as 22% to 27% with adenocarcinoma, central tumors, or if clinical N1 disease is present [62,68–70].

PET has been shown consistently to be more accurate than CT. In a recent meta-analysis, the median sensitivity and specificity of PET were 85% and 90%, respectively, compared with 61% and 79% for CT (P<.001) [63]. If lymph nodes were enlarged on the CT scan, the sensitivity of PET increased to 100% (range 90%–100%), but the specificity decreased to 78% (range 68%–100%). If the lymph nodes were not enlarged on CT scan, the sensitivity was 82% (range 65%–100%) with a specificity of 93% (range 92%–100%) [63]. Three other meta-analyses reported similar outcomes, with overall false positive rates of 13% to 22% and false negative rates of 5% to 7% [51,64,65]. Given the high false positive rate, confirmation of a positive PET scan result with a tissue diagnosis generally is recommended if the patient otherwise would be a surgical candidate [71]. Whether to accept a negative PET result remains controversial; however,

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Test</th>
<th>No. of patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toloza et al [51]</td>
<td>CT</td>
<td>3438</td>
<td>0.57</td>
<td>0.82</td>
<td>0.56</td>
<td>0.83</td>
<td>0.28</td>
</tr>
<tr>
<td>Toloza et al [51]</td>
<td>PET</td>
<td>1045</td>
<td>0.84</td>
<td>0.89</td>
<td>0.79</td>
<td>0.93</td>
<td>0.32</td>
</tr>
<tr>
<td>Toloza et al [51]</td>
<td>EUS—without biopsy</td>
<td>163</td>
<td>0.78</td>
<td>0.71</td>
<td>0.75</td>
<td>0.79</td>
<td>0.50</td>
</tr>
<tr>
<td>Toloza et al [76]</td>
<td>EUS—with needle biopsy</td>
<td>215</td>
<td>0.88</td>
<td>0.91</td>
<td>0.98</td>
<td>0.77</td>
<td>0.69</td>
</tr>
<tr>
<td>Toloza et al [76]</td>
<td>TBNA</td>
<td>910</td>
<td>0.76</td>
<td>0.96</td>
<td>1.00</td>
<td>0.71</td>
<td>0.70</td>
</tr>
<tr>
<td>Toloza et al [76]</td>
<td>Cervical mediastinoscopy</td>
<td>5687</td>
<td>0.81</td>
<td>1.00</td>
<td>1.00</td>
<td>0.91</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Abbreviations: EUS, endoscopic ultrasound; TBNA, transbronchial needle aspiration.
with a false negative rate of 5% to 7%—which may be higher if the lymph nodes are enlarged on CT scan—many are not comfortable accepting PET data alone, especially if the incidence of occult metastatic nodal disease is predicted to be high based on tumor type (adenocarcinoma), location (central tumors), or the presence of clinical N1 disease [3,5].

Because PET and CT can provide complementary information, integrated PET/CT scanners have been developed that allow fusion of the anatomic information that is provided by CT with the functional information that is provided by PET. Preliminary experience with these scanners in the staging of NSCLC has been promising. The accuracy of T, N, and M staging has been higher with PET/CT than with PET or CT alone [72–74]. In a series of 50 patients, PET/CT was more accurate in establishing the T stage compared with CT alone (\( P = .001 \)), PET alone (\( P < .001 \)), and the visual correlation of PET and CT (\( P = .013 \)) [72]. Likewise, PET/CT also was more accurate in N staging compared with PET alone (\( P = .013 \)) and the visual correlation of PET and CT (\( P = .021 \); however, false negative nodal staging remains a problem with this modality given the inability to detect microscopic lymph node metastases [72].

The gold standard for establishing the presence of N2 or N3 disease remains a cervical mediastinoscopy (Table 5) [75]. The average sensitivity of mediastinoscopy is approximately 80%, with a false negative rate of 9% to 10% [75,76]. False negative results usually are due to the presence of nodal disease in stations that are not easily accessible through a mediastinoscopy, including the posterior subcarinal lymph node (station 7), inferior mediastinal lymph nodes (stations 8 and 9), aortopulmonary (AP) window, and anterior mediastinal lymph nodes (stations 5 and 6) [75]. An extended cervical mediastinoscopy and an anterior mediastinotomy (Chamberlain procedure) are techniques that allow evaluation of the AP window lymph nodes (station 5). The false negative rates for both procedures range between 9% and 11% [75].

Other strategies that allow histologic confirmation of N2 or N3 disease include thoracoscopy, TTNA, bronchoscopy with a transbronchial needle aspiration (TBNA/Wang needle aspiration), and endoscopic ultrasound (EUS) with fine needle aspiration (FNA) [76]. All are most effective in the evaluation of enlarged lymph nodes and are associated with high false negative rates. Thoracoscopy and EUS allow sampling of nodal stations that may not be accessible through a standard cervical mediastinoscopy. In particular, EUS allows access to the AP window, and subcarinal and inferior mediastinal lymph nodes [75]. The overall average sensitivity of EUS is 78%; this increases to 90% with the addition of FNA [51,76]. The false negative rates for both procedures are 23% and 21%, respectively [51,76]. Using EUS-FNA to evaluate PET-positive lymph nodes may improve the false negative rate [77]. Bronchoscopy with TBNA is most useful for evaluating subcarinal nodes, but also can be used to evaluate right and left paratracheal space lymph nodes, which cannot be accessed through EUS [75]. The average sensitivity of this procedure is 75% with a false negative rate of 30% [76]. TTNA also can be used to confirm N2 or N3 disease, with a reported sensitivity of 90% and a false negative rate of 22% [76].
Staging small cell lung cancer

The TNM system is used rarely in the staging of SCLC. The two-stage system that initially was proposed by the Veterans Administration Lung Cancer Study Group remains the most commonly used system [78]. Patients who have disease that is limited to one hemithorax and regional lymph nodes are defined as having limited-stage disease; remaining patients are defined as having extensive-stage disease. There has been debate about how to stage patients who have contralateral mediastinal or supraclavicular lymph node involvement, or malignant pleural effusions. The International Association for the Study of Lung Cancer published a consensus report in 1989 which recommended that patients who have contralateral mediastinal and supraclavicular disease or ipsilateral malignant pleural effusions should be approached as having limited-stage disease [79].

Approximately two thirds of patients who have SCLC present with extensive-stage disease [7,58]. Because most patients are symptomatic at presentation, the clinical evaluation is less helpful in deciding whether to pursue extrathoracic staging studies [58]. In addition to a CXR, history, and physical examination, most patients should have routine blood work, including a complete blood cell count and serum chemistries with liver function tests, alkaline phosphatase, and lactate dehydrogenase. Imaging tests of the abdomen and brain, as well as bone scan frequently are included also in the staging evaluation. Richardson and colleagues [7] from the Navy Medical Oncology Branch developed a staging algorithm for SCLC that approached this evaluation in a sequential manner; testing was stopped after extensive-stage disease was confirmed. After an initial diagnostic evaluation, imaging of the brain in patients who had neurologic symptoms and a biopsy of soft tissue disease identified 60% of patients who had extensive-stage disease. After a subsequent bone scan and evaluation of the abdomen, 94% of the patients who had extensive-stage disease were identified. This sequential approach resulted in a substantial cost savings compared with a complete staging work-up.

Routine imaging of the brain and bone marrow biopsy also have been included in the extrathoracic staging evaluation of a patient who has SCLC [58,80]. The likelihood of a positive result with either evaluation is low if the clinical evaluation is negative and no other sites of extrathoracic metastatic disease have been identified. Approximately 10% to 20% of patients have brain or bone marrow involvement at presentation [58,80]. The false negative rate of the clinical evaluation in identifying brain metastases was reported to be approximately 5% (range 3%–9%) [58]. Likewise, the likelihood of finding bone marrow involvement as the only site of extrathoracic metastatic disease is less than 5% [58,80]. Therefore, the usefulness of either evaluation is low in a patient who has had a negative clinical and staging work-up for other sites of distant metastases. Routine imaging of the brain in asymptomatic patients was recommended by some investigators to avoid the development of irreversible neurologic signs and symptoms in patients who had a false negative clinical evaluation [80].
contrast, a routine bone marrow examination rarely is considered to be part of the standard staging evaluation [58].

PET has not been studied as extensively in staging patients who have SCLC; however, several series showed PET to be accurate in identifying the primary tumor and sites of metastatic disease [81–83]. In series of patients whose staging work-up was negative with standard testing, PET identified undetected sites of metastatic disease in 13% to as many as 50% of patients [81–83]. In addition, PET was helpful in planning radiation treatment by identifying additional sites of disease within the chest [81].

Summary

The approach to the diagnostic and staging evaluation of a patient who is suspected of having lung cancer begins with the clinical evaluation and initial chest imaging. Subsequent testing should proceed in a rational manner, based on information that was obtained in this initial evaluation. Newer modalities, like PET and EUS, can be helpful in selected situations. Of these modalities, PET has been studied the most extensively and is being used increasingly in the diagnostic and staging evaluation of patients who have this disease; however, like any test, PET has its limitations. The accuracy of PET in evaluating an SPN or lung mass establishes the role of PET in this setting. The high false positive and false negative rates in the evaluation of the mediastinum limit its usefulness in mediastinal staging, although PET information can be used to guide invasive diagnostic procedures. In the staging of NSCLC, PET seems to have a role in the evaluation of potential metastatic sites that were identified on initial testing. The routine use of PET in the preoperative staging for all resectable patients who do not have clinical evidence for metastatic disease has not been as well established. PET was cost effective in the preoperative staging of patients who had normal-sized mediastinal lymph nodes. In one randomized trial, routine use of PET before surgery resulted in a significant decrease in the rate of futile thoracotomies (benign lung lesions, pathologic N2 or N3 involvement, exploratory thoracotomy, recurrent disease or death within 1 year) compared with conventional staging (41% versus 21%, conventional work-up versus PET, \( P = .003 \)) [84,85]. In a more recent randomized comparison of up-front PET versus conventional staging, PET had similar accuracy and did not decrease the number of staging procedures that was required [86]. In this trial, PET did shorten the overall staging time by 9 days. Ultimately, the selected use of PET in preoperative staging seems most reasonable. Given the difference in the incidence of distant metastatic disease based on clinical stage, routine use of PET in patients who have clinical stage III disease and selected patients who have clinical stage II disease is justified [3,49]. Fusion PET/CT scanners may increase the accuracy of this modality, particularly with respect to T staging. PET also is a promising staging modality for small cell disease, but experience is limited; further trials are necessary before PET can be recommended routinely for use in this setting.
References


Clinical evaluation and staging