Non-small cell lung cancer (NSCLC) in the United States will continue to be a major public health issue, particularly as our elderly population grows. As surgery offers the best hope of cure for NSCLC, staging of NSCLC is critical because it directly impacts on the management of lung cancer. Cost, quality of life, safety, and accuracy of various staging methods all influence the clinical outcome. Staging of NSCLC is evolving due to the emergence of new and improved technologies. The objective of this article is to review the current methods used in staging of NSCLC. Currently, positron emission tomography and endoscopic ultrasound (EUS) show promise in identifying patients that may benefit from surgery. Histologic confirmation via EUS-guided fine-needle aspiration, however, may still be necessary to accurately stage the mediastinum.

Key words: endoscopic ultrasound; mediastinal lymph nodes; mediastinoscopy; non-small cell lung cancer; staging; thoracotomy

Abbreviations: EUS = endoscopic ultrasound; FNA = fine-needle aspiration; NSCLC = non-small cell lung cancer; PET = positron emission tomography; TEE = transesophageal echocardiography

Lung cancer is the number-one cancer killer of men and women in our nation. Lung cancer accounts for 28% of annual cancer deaths in the United States, and the cost to our nation was $35 billion in 1990. In 1999, lung cancer was diagnosed in 177,000 patients. Unfortunately, the majority of cases are diagnosed in late stages. Although surgery offers the best hope of cure for patients with non-small cell lung cancer (NSCLC), only one fourth of cases (44,250 patients) were eligible for surgery in 1993. The 5-year survival rate for patients undergoing surgery is a disappointing 41.4%. Once surgical candidates are selected, the success of surgery hinges on accurate staging. Consequently, futile surgeries impact negatively on cost, quality of life, and patient morale.

On December 15, 1999, the American College of Chest Physicians recommended the use of lung CT to screen female smokers > 60 years old. Despite the absence of data supporting its utility as a screening tool, physicians are already using lung CT to screen for lung cancer in men and women regardless of age. It is anticipated that as many as 2,700 patients per 100,000 people in the general population will present for lung cancer staging and possible surgery. The cost of lung cancer management may financially cripple our health-care system if management is not streamlined. New developments in lung cancer staging, such as positron emission tomography (PET) and endoscopic ultrasound (EUS) are well timed. The role of EUS and histologic confirmation will be addressed.

Detection of NSCLC metastases to various mediastinal lymph node stations is the challenge of re-
CT staging. Figure 1 demonstrates a posterior view of the posterior mediastinal lymph nodes. Multiple lymph node station involvement predicts a poor prognosis. Patients with N1 or N2 disease may benefit from surgery, while patients with N3 disease do not. Approximately 21 to 50% of NSCLC patients have metastases to mediastinal lymph nodes. In a prospective study of Arita et al., 28% (11 of 40 operable NSCLC patients) actually had N2 disease at surgery, and 64% (7 of 11 patients) had normal-sized lesions on transesophageal echocardiography (TEE). The posterior mediastinal lymph nodes (Fig 1) are seen with TEE. It is important to identify patients with N2 disease, as they may benefit from neoadjuvant therapy. Certainly, N2 disease can exist without N1 disease in up to 30% of cases.

CT is a routine test used in the initial evaluation of lung cancer. It is often useful in detecting the local extent of pulmonary disease and the presence of pleural effusions. However, CT is not reliable in mediastinal lymph node staging in patients with NSCLC. Due to signal averaging and inadequate contrast within the mediastinum, only lymph nodes > 1 cm in size are reliably detected. When compared to surgical findings, the sensitivity of CT in detecting metastases to mediastinal lymph nodes ranges from 45.5 to 84.4%. Similarly, the specificity has a wide range of 57 to 84.1%. When complete mediastinal lymph node dissection is performed during thoracotomy, the sensitivity of CT decreases to 60 to 79% and specificity decreases to 60 to 65%. The false-negative rate of metastases to mediastinal lymph nodes on CT ranges from 73.6% to 7% Historically, CT was found to overstaging 22.5% of patients and understage 19.4% of patients. The sensitivity of CT is higher in the right paratracheal lymph region (station 4R) than in the subcarinal region (station 7) or left mediastinum (Fig 1). However, CT does not readily detect malignant or benign lymph nodes in the paraesophageal region (station 8), subcarinal (station 7) or tracheobronchial regions (Fig 1). The lowest accuracy of CT staging was noted for left-sided and central lung tumors.

Although enlarged mediastinal lymph nodes are considered positive on CT, size is not a good predictor of metastases. Small lymph nodes may harbor malignancy, and lymph nodes > 1 cm in size are often benign. The prevalence of N2 disease ranges from 24.9 to 62%. In addition, metastases to mediastinal lymph nodes are not always enlarged. In a prospective study of Arita et al., 28% (11 of 40 operable NSCLC patients) actually had N2 disease at surgery, and 64% (7 of 11 patients) had normal-sized lesions on transesophageal echocardiography (TEE). The posterior mediastinal lymph nodes (Fig 1) are seen with TEE. It is important to identify patients with N2 disease, as they may benefit from neoadjuvant therapy. Certainly, N2 disease can exist without N1 disease in up to 30% of cases.

Interventional radiologists are able to obtain a fine-needle aspiration (FNA) of middle mediastinal lesions under CT guidance using a 19- to 22-gauge needle inserted through the right paratracheal space or suprasternal area. Lymph nodes in the subcarina are most often accessed by this method. Belfiore and colleagues precluded 9 of 19 patients (47%) from surgery using CT-guided FNA of mediastinal lesions. CT-guided biopsy of mediastinal lesions, however, is not without risks. Pneumothorax occurred in 16 of 84 patients (19%), and required chest tube placement in 3 patients after FNA of mediastinal lymph nodes and masses. A smaller study (n = 18) reported a pneumothorax rate of 22% following mediastinal lymph node biopsy in station 7 (subcarina), station 4 (lower paratracheal), and station 6 (ascending paraaortic) an anterior mediastinal lymph node
guided FNA of mediastinal lymph nodes is highly operator dependent and not widely available.

**Transbronchial Needle Aspiration**

A Wang 18-gauge transbronchial biopsy needle (Bard Endoscopic; Billerica, MA) is safe, and can be used to blindly aspirate mediastinal lymph nodes transbronchially during the initial evaluation of lung cancer with bronchoscopy. In 29 patients with lung cancer and mediastinal adenopathy on CT, the sensitivity of a Wang 18-gauge needle in mediastinal staging of NSCLC was 82%. Prior knowledge of the location of suspicious mediastinal lymph nodes, however, is important in obtaining a representative lymph node biopsy. This method is particularly useful in sampling subcarinal lymph nodes. This method is operator dependent and not commonly utilized.

**Endobronchial Ultrasound**

Endobronchial ultrasound is a fairly new technique performed by pulmonologists. The depth of imaging is 1.75 cm; hence, mediastinal lymph nodes are not readily visualized. No difference was seen between transbronchial and endobronchial ultrasound-guided FNA. The sensitivity and specificity for endobronchial ultrasound are 82.6% and 100%, respectively, for sonographically visualized lymph nodes. Experience with this method is still limited.

**MRI**

MRI is not reliable for detecting mediastinal involvement. It is useful, however, in detecting pericardial involvement. The sensitivity and specificity of MRI in detecting metastases to mediastinal lymph nodes ranges from 52 to 65% and from 48 to 79%, respectively. When compared to CT, MRI does not have better spatial resolution, and it is limited by motion artifact. In addition, patients often complain of claustrophobia. Previous studies have failed to show accurate radiographic, surgical, and pathologic correlation. Both CT and MRI are unable to detect micrometastases in mediastinal lymph nodes.

**PET**

The use of PET in staging NSCLC has recently received attention due to its ability to detect micrometastases. PET scanning uses a radionuclide, 2-18fluoro-2-deoxy-d-glucose, which competes with glucose, and is taken up by cells that have a high metabolic rate such as cancer and inflammatory cells. Once taken up by cells, 2-18fluoro-2-deoxy-d-glucose is not metabolized or secreted out of the cell, and the isotope can be detected by PET. Due to poor count recovery in small lesions, detecting malignancy in lesions < 1 cm in size is not reliable. Several prospective studies show that PET is more accurate than CT in detecting metastases to mediastinal lymph nodes (Table 1). The sensitivity and specificity for PET in detecting metastases to mediastinal lymph nodes is high as shown in Table 1. The positive predictive value and negative predictive value of PET in detecting mediastinal lymph node metastases were shown to be 75% and 95.8%, respectively.

In patients with negative PET scan results, the false-negative rate of involved mediastinal lymph nodes was low; therefore, thoracotomy without further staging procedures was recommended. Up to 24% of the PET scans, however, are falsely positive in detecting mediastinal lymph node metastases. This could result in up to 24% of patients undergoing unnecessary neoadjuvant chemotherapy. Any inflammatory reaction or central lung tumors may be misinterpreted as mediastinal lymphadenopathy. Other factors that can result in false-positive PET scan results include the following: active tuberculosis, granulomas, pneumonia, abscess, sarcoidosis, and lymphoid hyperplasia.

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>PET Sensitivity</th>
<th>PET Specificity</th>
<th>CT Sensitivity</th>
<th>CT Specificity</th>
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<td>82</td>
<td>81</td>
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<td>Valk et al. 47 1995</td>
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<td>Chin et al. 50 1995</td>
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<tr>
<td>Bury et al. 48 1996</td>
<td>50</td>
<td>90</td>
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<td>Steinert et al. 52 1997</td>
<td>47</td>
<td>89</td>
<td>99</td>
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<td>94</td>
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</tbody>
</table>

*Data are presented as %.
inflammation in the setting of bronchiectasis and atelectasis, histoplasmosis, aspergillosis, blastomycosis, rheumatoid arthritis, tumor necrosis, radiation pneumonitis, and airway inflammation associated with asthma.\textsuperscript{53} False-positive PET scan results are known to occur after mediastinoscopy; thus, pathologic evaluation has been recommended in patients with positive mediastinal lymph nodes on PET scan.\textsuperscript{53} More data are needed in examining the role of PET with respect to normal-sized mediastinal lymph nodes. Drawbacks to the widespread use of PET include cost and access. The cost of a PET scanner is approximately $2 million, and an individual scan ranges from $900 to $2,080.\textsuperscript{54,55}

**Mediastinoscopy and Mediastinotomy**

Surgeons will perform mediastinoscopy if suspicious or enlarged lymph nodes are seen on radiographic imaging or CT. Some surgeons will perform mediastinoscopy routinely in the absence of radiographic abnormalities. Cervical mediastinoscopy is a surgical technique used to sample suspicious superior mediastinal lymph nodes and occasionally subcarinal lymph nodes. It is considered the standard of care in staging paratracheal, azygos, and subcarinal lymph nodes. Occasionally, subaortic lymph nodes and ascending para-aortic lymph nodes may also be sampled. The complication rate is approximately 1.7% and includes the following: pneumothorax and left recurrent laryngeal nerve injury, avulsion of the pulmonary artery branch, bleeding from blood vessels within the mediastinum, esophageal tear, cautery burn of the bronchus, wound infections, bleeding from a lymph node biopsy site, air leak, as well as risks of general anesthesia.\textsuperscript{56,57} Anterior mediastinoscopy, or mediastinotomy are useful in left upper lobe cancers when evaluating subaortic (station 5) and ascending para-aortic (station 6) [anterior mediastinal] lymph nodes. In addition, lymph nodes in the right paratracheal (R2) and right lower paratracheal (R4) are readily accessible by mediastinoscopy.

The sensitivity of mediastinoscopy in detecting metastases to accessible mediastinal lymph node ranges from 79 to 93\%.\textsuperscript{46,56,58} The specificity of mediastinoscopy in detecting mediastinal lymph node metastases was 100% in these studies. A negative cervical mediastinoscopy result correlates with a 53\% 5-year survival rate, and a positive cervical mediastinoscopy result correlated with a 4\% 2-year survival rate.\textsuperscript{56} The low 5-year survival rate in negative cervical mediastinoscopic findings may actually represent undetected advanced disease. In fact, 72\% of patients with mediastinal lymph node metastases at thoracotomy were found to have lymph nodes that were not accessible with mediastinoscopy.\textsuperscript{59} In addition, N2 disease was identified at thoracotomy in 14.7\% of NSCLC patients with a negative mediastinoscopic finding.\textsuperscript{59} Thus, advanced disease should still be considered in a patient with a negative mediastinoscopic finding. Most would agree, however, that mediastinoscopy is safe in experienced hands, and can appropriately preclude patients from unnecessary thoracotomy. Although mediastinoscopy is considered the standard of care, the use of this invasive surgical staging method is declining in favor of other staging modalities such as PET and EUS.

**EUS**

EUS is a unique minimally invasive procedure that offers great promise in staging mediastinal lymph nodes in NSCLC patients. Trained gastroenterologists perform EUS on an outpatient basis. Patients must be able to withstand conscious sedation for the procedure. Two types of EUS scopes are used and have a depth of imaging up to 10 cm (Fig 2). A radial...
scope has a 360° cross-sectional view, and a linear scope has a 180° sagittal view. A FNA is performed under real-time ultrasonography using pulse-wave and color Doppler to identify adjacent blood vessels.

EUS imaging is performed from the esophagus and stomach. Lymph nodes can be identified in the posterior mediastinum, retroperitoneum, and celiac regions. Posterior mediastinal lymph nodes are predominantly left sided and communicate with the para-aortic lymph nodes of the abdomen; hence, evaluation of the celiac region is important. In addition, metastases may be seen in the left adrenal gland and left lobe of the liver. The mediastinal lymph node stations that can be readily imaged by EUS include the following: subcarinal (station 7) [Fig 3, top], subaortic (station 5) [Fig 3, bottom], paraesophageal (station 8), inferior pulmonary ligament region (station 9), and main bronchial (station 10) [Fig 1].24,28,60–62 Lymph nodes in the left paratracheal (station 2) and left lower paratracheal (station 4) stations can be imaged and sampled, and are more accessible than the right paratracheal and lower paratracheal lymph nodes due to air interference from the trachea. Metastatic mediastinal lymph nodes were most often identified in the subcarina (station 7) and paraesophageal area (station 8) when evaluated by TEE.61 Unfortunately, lymph nodes that are far away from the esophagus, such as lobar (station 12) and interlobar (station 11), cannot be readily seen by EUS (Fig 1).28 This is one limitation of EUS. Likewise, lymph nodes anterior and lateral to the trachea (station 3, station 6) cannot be imaged reliably with EUS due to air interference.28 EUS is complementary to mediastinoscopy, as aortopulmonary window (station 5) and subcarinal (station 7) lymph nodes are stations readily accessed with EUS (Fig 1).25 Often, subcarinal lymph nodes cannot be accessed with mediastinoscopy.

Several prospective studies of patients with lung cancer demonstrate a sensitivity and specificity of EUS-guided FNA in detecting metastases to posterior mediastinal lymph nodes ranging from 88 to 96% and 80 to 100%, respectively.24,25,60–64 EUS-guided FNA is safe, and there have been no reports of complications or mediastinitis despite the absence of prophylactic antibiotics (Table 2).24,25,60–72 The sensitivity and specificity of EUS decrease, however, if FNA is not performed.24,60,62,64 Ultrasound criteria that are 60 to 80% predictive of lymph node metastases include the following: round shape, sharp distinctive border, homogenous hypoechoic echo

### Table 2—Operative Characteristics of EUS-Guided FNA and EUS Alone in the Detection of Mediastinal Lymph Nodes in Patients With Lung Cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Sensitivity</th>
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<td>Schuder et al,24†</td>
<td>32</td>
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<td>96</td>
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<tr>
<td>Fritscher-Ravens et al,68</td>
<td>35</td>
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<td>Giovannini et al62</td>
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<td>Hawes et al,61†</td>
<td>20</td>
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<td>Silvestri et al,23</td>
<td>27</td>
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<td>89</td>
<td>82</td>
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</table>

*Data are presented as %. PPV = positive predictive value; NPV = negative predictive value.
*EUS alone.
pattern, and short-axis diameter > 5 mm.\textsuperscript{71,73} Therefore, histologic confirmation is still essential. The presence of granulomatous disease or anthracosilicosis in the mediastinum also lowers the sensitivity and specificity of EUS if FNA is not performed.\textsuperscript{24}

Detection of micrometastases within normal-appearing mediastinal lymph nodes remains a challenging issue for EUS-guided FNA, as these micrometastases may be missed.\textsuperscript{25,64} In a prospective study of 20 patients with lung cancer, two of three metastatic lymph nodes measuring < 1 cm in diameter by EUS had a 2-mm focus of metastases within the lymph node.\textsuperscript{64} Despite these false-negatives results, EUS findings precluded 10% (2 of 20 patients) from unnecessary surgery due to metastases in the left lobe of the liver and celiac lymph nodes.\textsuperscript{64}

EUS significantly influences the management of patients with NSCLC. There were 59% (14 of 24 patients with NSCLC) precluded from surgery based on EUS-guided FNA results.\textsuperscript{64} Similarly, 18.5% (5 of 27 patients) were precluded from surgery because small cell lung cancer was diagnosed by EUS-guided FNA.\textsuperscript{25} EUS is valuable in making a diagnosis of mediastinal disease after a nondiagnostic bronchoscopy or transthoracic needle biopsy. In 35 patients with nondiagnostic bronchoscopic findings, EUS-guided FNA was 96% sensitive and 100% specific in obtaining a diagnosis, and was successful in making a diagnosis in lymph nodes < 1 cm in size.\textsuperscript{60} In this study, management of 66.6% of the malignant cases and 40% of the benign cases was impacted by the EUS findings, and these patients avoided further invasive tests.\textsuperscript{60} Thus, EUS is safe, accurate, and effective in evaluating mediastinal disease. Currently, there are no recommendations for the routine use of EUS in staging NSCLC; however, it should be considered in patients that are suspected to have advanced disease and may benefit from neoadjuvant therapy.

Evidence supports that we cannot afford to rely on radiographic staging alone, despite improved detail of radiographic techniques. Mediastinoscopy alone cannot stage the entire mediastinum. Ultimately, when inaccurate staging results in understaging, patients may be subjected to futile surgeries, and a missed opportunity for a neoadjuvant chemotherapy. When patients are overstaged, patients may undergo unnecessary neoadjuvant chemotherapy and possibly miss an opportunity for a curative resection. EUS is complementary staging tool in patients with NSCLC.

As the majority of patients present in late stages of lung cancer, EUS will likely be useful in precluding unnecessary surgeries. Histology plays an important role in accurate staging and cannot be eliminated. Lack of histologic, radiographic, and surgical correlation of mediastinal lymph nodes is a weakness of several studies that prevents external validity. In addition, routine screening for lung cancer is on the horizon, and will heighten the urgency of accurate staging. Hence, reevaluation of minimally invasive staging strategies for NSCLC staging is timely, and larger randomized prospective studies comparing EUS with existing NSCLC staging tools with attention to histologic correlation, clinical outcome, cost, and quality of life should be pursued prior to further formal recommendations.

References


