Use of Endobronchial Ultrasound and Endoscopic Ultrasound to Stage the Mediastinum in Early-Stage Lung Cancer

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Abstract
Lung cancer remains the deadliest cancer, with more than 160,000 deaths and 226,000 newly diagnosed cases estimated in 2012. Because treatment and survival are directly linked to disease stage, accurate staging in all patients is crucial. The proper staging of early-stage lung cancer involves investigation for the presence of metastatic spread via lymph nodes within the thorax. Initial steps include CT and PET. Mediastinoscopy has previously been considered the gold standard for mediastinal lymph node sampling; however, over the past 10 years the use of ultrasound-guided lymph node sampling has been shown to be at least as sensitive, and has the added advantage of being able to access significantly more stations. This article reviews the current standards of lung cancer staging in 2012. (JNCCN 2012;10:1277–1282)

NCCN: Continuing Education

Learning Objectives
Upon completion of this activity, participants will be able to:
• Describe the current strategies for staging of the mediastinum in early-stage lung cancer.
• Describe the role of EBUS-TBNA and EUS-FNA in the staging of lung cancer.
Lung cancer and its related complications remain the leading cause of cancer-related deaths in the United States. In 2012, an estimated 226,000 new cases of lung cancer will be diagnosed and 160,000 deaths from the disease are expected to occur. Lung cancer is generally divided into 2 main groups: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), with NSCLC accounting for more than 85% of cases. Various prognostic factors may help predict survival in patients with NSCLC, but the presence of early-stage disease and the ability to undergo surgical resection offers the best chance for long-term cure.

Initial Evaluation

The initial evaluation of lung cancer often involves the use of CT and PET in an attempt to radiologically define disease burden. In the most recent consensus statement by the American College of Chest Physicians (ACCP), Silvestri et al illustrated the wide variation with CT in both sensitivity of detecting advanced disease (20%–96%) and its poor negative predictive value (47%–96%). Unfortunately, very similar data exist for the use of PET scanning, with a wide variation in the both the sensitivity of detecting advanced disease (40%–100%) and its negative predictive value (50%–100%). Lymph node enlargement identified on CT can be associated with false-positive rates of up to 40%, and false-positive rates from PET scanning have been documented in the 15% to 20% range. Even more disappointing is the 20% to 28% false-negative rate of PET when specifically evaluating patients for more advanced nodal disease (N2/N3).

Because of these limitations, the ACCP, American Thoracic Society, and European Society of Thoracic Surgery mandate pathologic staging for all patients who may be candidates for surgical resection.

However, a subset of the lung cancer population remains that may be referred directly to surgery. Most experts still agree that patients with peripheral clinical stage I tumors whose PET scan is negative in the mediastinum and are good operative candidates should proceed straight to surgical resection, with surgical lymph node sampling. Invasive staging of the mediastinum is still recommended for patients who have PET evidence of N1 disease.

However, the false-negative rate of PET/CT scanning for early-stage disease is approximately 8% to 10%. This begs the question of whether every patient should undergo some type of mediastinal evaluation before surgical resection. Until more data become available regarding the outcome of patients who receive neoadjuvant therapy for stage IIIa (N2) disease compared with those who are found to have N2 disease at the time of resection and receive adjuvant therapy, most institutions and professional guidelines continue to endorse that those with suspected early-stage NSCLC and low suspicion of advanced nodal disease be referred straight to the operating theater for resection and lymph node dissection.

Current Strategies for Staging the Mediastinum

Mediastinoscopy had been considered the “gold standard” for evaluation of the mediastinum. However, mediastinoscopy has several limitations, and as newer methods become more available, efficient, and standardized, the process of NSCLC staging will continue to evolve. The next sections briefly describe the procedures of mediastinoscopy, transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), and the current literature supporting these methods.

Mediastinoscopy

Mediastinoscopy is typically performed by a thoracic surgeon as an outpatient procedure under general anesthesia. A 2- to 3-cm incision is made above the suprasternal notch and, after blunt dissection into the pretracheal space, a mediastinoscope is introduced. The mediastinoscope allows for visualization of the pretracheal space and associated lymph nodes. Standard mediastinoscopy allows access to the lymph nodes located in nodal stations 2, 4, and 7, but not access to stations 5 and 6 (aortopulmonary window nodes), nor does it routinely offer access to the hilar lymph nodes (stations 10–12). Although previously considered the gold standard, it can still have a 9% to 11% false-negative rate. If needed, stations 5 and 6 can be sampled via an anterior mediastinoscopy (Chamberlain procedure), extended cervical mediastinoscopy, or video-assisted thoracoscopic surgery (VATS). One of the most shocking statistics was from a survey of 729 hospitals treating more than 40,000 patients with lung cancer, which found that mediastinoscopy was performed in only 27% of patients under-
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Going surgical resection of lung cancer. In the patients in whom it was performed, adequate nodal tissue was obtained in fewer than 50% of these cases.\(^\text{11}\) Importantly, thoracic surgeons sample mediastinal lymph nodes much more frequently than general surgeons, and the authors highly recommend that thoracic surgeons specifically be part of the multidisciplinary thoracic oncology team.

Although still used by many thoracic oncology departments, mediastinoscopy use has significantly decreased over the past 10 years, with a shift toward the use of endoscopic staging procedures. Multiple multidisciplinary national organizations now support endoscopic ultrasound of the mediastinum as an effective method of noninvasively staging the mediastinum and evaluating patients for potential surgical resection. The European Society for Medical Oncology (ESMO) currently recommends the need for further tissue sampling of any abnormal lymph node visualized on PET/CT imaging (grade 1A). However, they do not offer a distinction between the method of evaluation (ie, conventional TBNA, EBUS-TBNA, EUS-FNA, or mediastinoscopy).\(^\text{7}\) The ACCP also currently recommends the use of endoscopic ultrasound-guided procedures for staging of the mediastinum.\(^\text{5}\)

**EUS-FNA**

EUS-FNA is an outpatient procedure typically performed by gastroenterologists. A specially designed gastroscope that incorporates a curvilinear array ultrasound transducer at the distal tip is introduced through the mouth/oropharynx into the esophagus and stomach. The procedure is often performed within an endoscopy suite and can be accomplished with moderate or deep sedation. Real-time ultrasound is used to visualize the abnormal lymph nodes and needle aspiration is performed under ultrasound guidance. Needle size can vary from 19- to 25-gauge. EUS-FNA is recommended for accessing abnormal lymphadenopathy in stations 2L, 4L, 5, 7, 8, and 9. The right-sided pretracheal (2R and 4R) lymph nodes may be more difficult to sample, but numerous studies have identified these areas to be accessible (see later discussion).

**EBUS-TBNA**

EBUS-TBNA is typically performed by pulmonologists or thoracic surgeons, and like EUS-FNA, the bronchoscope has a curvilinear ultrasound probe at its tip allowing for real-time ultrasound-guided needle aspiration with specially designed 21- or 22-gauge needles. This procedure can also be performed in an endoscopy suite under moderate or deep sedation. EBUS-TBNA allows access to most lymph nodes located with the thorax, including stations 2, 3, 4, 7, 10, 11, and 12.

### Current Literature Supporting EUS and EBUS

All staging procedures should be performed with an attempt to identify disease in the highest possible nodal station or prove distant disease. For example, with either EUS or EBUS, one should always attempt to sample possible M1 (EUS of the left adrenal if FDG-avid) or N3 disease first, followed by N2, then N1. This strategy is designed to eliminate the risk of upstaging patients as a result of contamination of specimens with tumor cells from a positive lower-stage lymph node. This strategy also attempts to minimize the number of procedures and biopsies performed, because if a N3 lymph node is identified with carcinoma, then both a diagnosis (cancer) and stage (at least stage IIIB) have been identified. No further need exists to perform biopsies of the lung mass/nodule, and therefore the risk of transbronchial/bronchial biopsy can be avoided.

In one of the first trials assessing EBUS-TBNA for the evaluation of potentially resectable NSCLC patients, 102 patients underwent CT imaging, PET imaging, and EBUS-TBNA. No patients underwent further surgical staging in this study, but rather went straight to resection if no evidence of N2 or N3 disease was noted on EBUS-TBNA. When compared with surgical resection with mediastinal lymphadenectomy, EBUS-TBNA showed a sensitivity and specificity of 92.3% and 100% with a positive predictive value, negative predictive value, and diagnostic accuracy of 100%, 97.4%, and 98%, respectively, which were significantly better than with CT or PET imaging.\(^\text{11}\)

Data regarding the efficacy of endoscopic ultrasound sampling continues to accrue. One of the largest studies of EBUS-TBNA that identified 572 lymph nodes in 500 patients showed a diagnostic yield of 94%.\(^\text{11}\) The biopsy specimens were taken from multiple nodal stations, including hilar and mediastinal areas. Lymph nodes in region 2L (40 nodes), 2R (53 nodes), 3 (35 nodes), 4R (86 nodes), 4L (77 nodes), 7 (127 nodes), 10R (38 nodes), 10L (43 nodes), 11R (40 nodes), and 11L (33 nodes) were all sampled with a sensitivity of 94%, a specificity of 100%, and a positive predictive value of 100% calculated per patient. No complications were recorded.
EBUS has also been shown to be at least as good if not better than mediastinoscopy as an initial staging procedure. A prospective crossover trial of cervical mediastinoscopy and EBUS-TBNA was performed in 66 patients undergoing surgical resection for NSCLC. EBUS-TBNA showed an improved sensitivity and diagnostic yield over cervical mediastinoscopy when followed by surgical resection.\textsuperscript{13} EBUS was especially useful for lymph nodes in posterior station 7, where they were inaccessible to mediastinoscopy. Additionally, no complications were seen after EBUS-TBNA, whereas 7.5% of patients undergoing mediastinoscopy experienced complications (bleeding and infection). Another prospective trial comparing 153 patients requiring mediastinoscopy before surgical resection for NSCLC evaluated the agreement in lymph node sampling between EBUS-TBNA and mediastinoscopy. Each patient underwent EBUS-TBNA immediately followed by mediastinoscopy, and if both were negative for disease, then surgical resection with lymph node dissection was performed. No significant differences were seen in sensitivity, specificity, negative predictive value, and diagnostic accuracy when comparing EBUS-TBNA versus mediastinoscopy.\textsuperscript{14}

EUS-FNA alone has also been compared with mediastinoscopy for evaluating suspected NSCLC for surgical resection. Tournoy et al\textsuperscript{15} evaluated 40 patients, randomizing them to surgical staging versus EUS-FNA (followed by surgical staging if EUS-FNA was nondiagnostic). The primary end point of this study, which was to reduce the need for surgical staging procedures, was successfully shown, with surgical staging reduced by 68% in those undergoing EUS-FNA.

More data continue to become available regarding the combined use of EBUS-TBNA and EUS-FNA in the evaluation of thoracic lymphadenopathy. Hwangbo et al\textsuperscript{16} investigated using the EBUS bronchoscope in both the airway and esophagus to obtain EBUS-TBNA and “endoscopic ultrasound with bronchosopic-guided FNA (EUS-B-TBNA)” to stage the mediastinum. A trend was seen for EUS-B-TBNA in improving the sensitivity, negative predictive value, and diagnostic accuracy over EBUS-TBNA alone, but the investigators also increased the number of nodes sampled. A similar study was performed by Herth et al,\textsuperscript{17} again using the EBUS bronchoscope in the airway and esophagus. They consecutively enrolled 150 patients with suspected or known NSCLC requiring mediastinal staging. EBUS-TBNA was diagnostic in 91%, EUS-FNA in 89%, and the combination in 96%. The combined use of EBUS-TBNA and EUS-FNA also had a higher negative predictive value (96%) when compared with the single modalities. Of the 68 patients with no evidence of advanced nodal involvement, only 1 (1.5%) had evidence of advanced nodal involvement at surgery or during follow-up.

In the largest, multicenter, randomized trial comparing endoscopic lymph node sampling (EBUS-TBNA and EUS-FNA) with mediastinoscopy, 241 patients with suspected early-stage NSCLC were randomized to either mediastinoscopy or endoscopic staging. As per international guidelines at the time of the trial, all nondiagnostic endoscopic evaluations were then followed by mediastinoscopy. The sensitivity was 79% for surgical staging, 85% for endoscopic staging, and 94% for combined endoscopic and surgical staging. The use of endoscopy was also able to decrease the number of unnecessary thoracotomies from 18% to 7% ($P = .02$).\textsuperscript{18} The overall rate of complications was similar in both groups.

Recent data also suggest that stereotactic body radiation therapy (SBRT) can produce excellent local control in medically inoperable patients with early-stage lung cancer.\textsuperscript{19} It is imperative to confirm lack of nodal spread in these patients if SBRT is to be successful. EBUS-TBNA has been shown to be an excellent modality for confirming lack of nodal involvement in patients receiving SBRT as definitive treatment.\textsuperscript{20} The big advantage of EBUS-TBNA in this group of patients is that the only other way to sample N1 nodes would be VATS, and because these patients are not surgical candidates, it would be unreasonable to put them through a surgical staging procedure. As SBRT is investigated for medically operable patients, future studies will be required to determine if surgical staging has any benefits over staging with EBUS-TBNA.

In 2012, it is no longer adequate to make a diagnosis of “lung cancer.” It is not even adequate to make a diagnosis of “non–small cell lung cancer” or even “adenocarcinoma.” Molecular testing is required to assess for predictive and prognostic tumor markers. One of the most important benefits of EBUS-TBNA is the ability to routinely obtain enough tissue to allow for testing of epidermal growth factor receptor, KRAS, and EML4-ALK gene mutations.\textsuperscript{21}
Cost of Endoscopic Bronchoscopy and Mediastinoscopy

Concerns regarding cost of procedures and need for hospitalization remain a significant impetus in future directions of providing health care. Both mediastinoscopy and bronchoscopy can currently be performed as outpatient procedures. Most costs now associated with these procedures are directly related to the procedure itself, anesthetic needs, and location of services provided. In general, mediastinoscopy requires general anesthesia in an operating room; however, it uses reusable equipment that would be available at most hospitals providing thoracic surgical care. Endoscopic ultrasound procedures do not require operating room time, nor do they require the use of anesthesia, but the needles and balloons used during each procedure are disposable. Additionally, more endoscopy units are performing both EUS-FNA and EBUS-TBNA with deep sedation, which lessens the cost advantage of endoscopic staging.

An Australian cost-analysis study confirmed the cost savings associated with the use of EBUS-TBNA in patients with NSCLC and thoracic lymphadenopathy. EBUS-TBNA was associated with a cost savings of $5721 per patient when compared with mediastinoscopy, and $799 when compared with conventional TBNA. Their cost-saving calculations included the assumption of zero complications from mediastinoscopy, which could potentially underestimate the savings.

Limitations of EBUS and EUS

It is important to recognize the limitations of EUS-FNA and EBUS-TBNA, and some authors still believe that EBUS should only be used in specific circumstances, with mediastinoscopy being the preferred staging procedure for routine staging. As with all procedures, EUS-FNA and EBUS-TBNA have distinct learning curves. Most patients in the studies discussed earlier showing the high yield of these procedures come from centers of excellence, and the results may not be easily extrapolated to lower-volume centers. In fact, case-volume has been shown to be an important factor determining the success of EBUS-TBNA. For convex-probe EBUS, in the hands of thoracic surgeons (who have a better understanding of extra-airway thoracic anatomy than most pulmonologists), there seems to be a learning curve of at least 10 procedures, and as with any procedure, it is necessary to have continuing volume to maintain the necessary skill. Additionally, as the false-negative rate can be as high as 14%, most experts still recommend that nondiagnostic lymph node aspirate samples should be followed by surgical staging procedures before resection. This is typically performed by VATS at the time of resection, but if the patient is a higher-risk surgical candidate, mediastinoscopy or even repeat EBUS can be performed. It is also important to note that the performance characteristics of EBUS-TBNA are worse for restaging after induction chemotherapy, with a sensitivity of 76%, a negative predictive value of 20%, and a diagnostic accuracy of 77%. This needs to be balanced because most surgeons do not like performing repeat mediastinoscopy after radiation therapy because of alteration of tissue planes and an increased risk of bleeding.

Conclusions

Endoscopic and endobronchial ultrasound-guided lymph node sampling have been found to be at least as effective as mediastinoscopy, while being less invasive and more cost-effective. They can now be considered the standard of care for mediastinal and hilar lymph node sampling. Both EUS-FNA and EBUS-TBNA can be accomplished in outpatient endoscopy suites with moderate sedation and can decrease the need for surgical staging. Mediastinoscopy or other surgical staging is recommended for all patients undergoing resection with curative intent who have negative results after endoscopic lymph node sampling (EBUS-TBNA and EUS-FNA), because false-negative results may occur with these minimally invasive techniques.

References


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Post-Test Questions

1. True or False: Mediastinoscopy is recommended for all patients undergoing resection with curative intent who have negative results after endoscopic lymph node sampling (EBUS-TBNA and EUS-FNA), because false-negative results may occur with these minimally invasive techniques.

2. Which of the following is true about EBUS-TBNA?
   a. EBUS-TBNA is typically performed by pulmonologists or thoracic surgeons.
   b. It can be performed in an endoscopy suite under moderate or deep sedation.
   c. It allows access to most lymph nodes located with the thorax, including stations 2, 3, 4, 7, 10, 11, and 12.
   d. All of the above.

3. True or False: EBUS cannot be used to obtain tissue for molecular testing (for example, epidermal growth factor receptor mutations or ALK gene rearrangements).