Endobronchial ultrasound and endoscopic ultrasound-guided lymph node biopsy may represent an alternative to cervical mediastinoscopy.

Minimally Invasive Mediastinal Staging of Non–Small-Cell Lung Cancer: Emphasis on Ultrasonography-Guided Fine-Needle Aspiration

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Background: Mediastinal staging in patients with non–small-cell lung cancer (NSCLC) is crucial in dictating surgical vs nonsurgical treatment. Cervical mediastinoscopy is the “gold standard” in mediastinal staging but is invasive and limited in assessing the posterior subcarinal, lower mediastinal, and hilar lymph nodes. Less invasive approaches to NSCLC staging have become more widely available.

Methods: This article reviews several of these techniques, including noninvasive mediastinal staging of NSCLC, endobronchial ultrasound (EBUS) and fine-needle aspiration (FNA), endoscopic ultrasound (EUS) and FNA, and the combination of EBUS/EUS.

Results: Noninvasive mediastinal staging with computed tomography and positron-emission tomography scans has significant false-negative and false-positive rates and requires lymph node tissue confirmation. FNA techniques, with guidance by EBUS and EUS, have become more widely available. The combination of EBUS-FNA and EUS-FNA of mediastinal lymph nodes can be a viable alternative to surgical mediastinal staging. Current barriers to the dissemination of these techniques include initial cost of equipment, lack of access to rapid on-site cytology, and the time required to obtain sufficient skills to duplicate published results.

Conclusions: Within the last decade, these approaches to NSCLC staging have become more widely available. Continued study into these noninvasive techniques is warranted.

Introduction

Assessment of the mediastinum is a crucial component in the initial staging of patients with newly diagnosed non–small-cell lung cancer (NSCLC) and is important for the documentation of recurrent disease. The results of mediastinal staging often dictate whether a patient is a candidate for surgical treatment options.

Prior to the mid-2000s, the primary means of diagnosis and tissue procurement within the mediastinum was cervical mediastinoscopy or open surgical procedures. Cervical mediastinoscopy continues to maintain low morbidity rates, generally ranging from...
Noninvasive mediastinal staging modalities include contrast-enhanced CT scan and fluorodeoxyglucose (FDG) PET-CT, but each of these approaches has limitations in differentiating benign from malignant lymph nodes. Of the noninvasive staging modalities, CT and FDG PET-CT have moderate reliability when staging NSCLC. When using the standard short-axis lymph node diameter of ≥ 10 mm, the sensitivity of CT is 55% and specificity is 81% in differentiating benign from malignant mediastinal lymph nodes. In fact, earlier studies utilizing CT scan alone have demonstrated that more than 40% of mediastinal lymph nodes > 15 mm were benign and 15% of mediastinal lymph nodes ≤ 10 mm were malignant.

Fischer et al demonstrated that the combined radiographic adjunct of PET-CT resulted in a decrease in the total number of what they described as “futile thoracotomies,” i.e., mediastinal node involvement at thoracotomy, benign disease, or patients who died or experienced recurrent disease within 1 year of initial thoracotomy, from 52% with conventional imaging to 35% with PET-CT scan. Additionally, FDG PET-CT detects distant metastases in 10% to 15% of patients and identifies lymph node metastasis in 10%. PET-CT has a false-negative rate of 20% for small lymph nodes and a 20% false-positive rate for large lymph nodes. The American College of Chest Physicians (ACCP) Guidelines for Diagnosis and Management of Lung Cancer (3rd edition) pooled analyses revealed a sensitivity and specificity of 62% and 90%, respectively, for PET-CT and recommended “abnormal findings must be confirmed by tissue biopsy to ensure accurate staging.” Thus, invasive testing is usually still required for proper staging, given the false-negative and false-positive rates of CT and FDG PET-CT.

In the last decade, less invasive approaches to NSCLC staging have become more widely available. Both the ACCP and the European Society of Thoracic Surgery (ESTS) stated in 2007 that mediastinoscopy is the standard of care to investigate lymph node stations 2R (upper right paratracheal), 2L (upper left paratracheal), 4R (lower right paratracheal), 4L (lower left paratracheal), and 7 (subcarinal); however, EUS-guided fine-needle aspiration (FNA) and EBUS-guided transbronchial needle aspiration (TBNA) were deemed optional investigative modalities to evaluate for nodal metastasis. Since 2007, needle biopsy techniques such as EUS-FNA, EBUS-TBNA, and combined EBUS-TBNA/EUS-FNA have become the preferred methods to obtain tissue, with sensitivities of 89%, 89%, and 91%, respectively.

**Endobronchial Ultrasound and Fine-Needle Aspiration**

EBUS has been performed since the early- to mid-1990s, with increasing reports of utilization and comparison to cervical mediastinoscopy dating back into the early 2000s. Bronchoscopic EBUS is performed as an adjunct procedure following routine bronchoscopy, most commonly using intravenous conscious sedation. The EBUS bronchoscope is equipped with a linear probe ultrasound at the tip, which allows for visualization of mediastinal structures including lymph nodes, vasculature, and stromal tissue. EBUS also allows for real-time direct visualization of mediastinal node puncture and subsequent aspiration.

After completion of a routine airway survey, the EBUS bronchoscope is inserted, the nodal station of interest is localized, and sequential sampling is performed. Initial sampling sites are usually dictated by PET-CT imaging and generally are used for disease stage documentation, followed potentially by additional cytological specimens for molecular analysis. Rapid on-site cytological examination is typically performed during the procedure. The addition of EBUS following routine bronchoscopy adds approximately 15 to 30 minutes to each procedure, depending on the number of nodal stations sampled. In addition to the mediastinal nodal stations (2R, 2L, 4R, 4L, and 7) accessible by cervical mediastinoscopy, the hilar, interlobar, and lobar nodes (levels 10, 11, and 12, respectively) are also accessible. In a recent head-to-head comparison of EBUS and mediastinoscopy, Yasufuku et al prospectively evaluated 153 patients who underwent EBUS and cervical mediastinoscopy in back-to-back procedures and demonstrated a specificity and positive predictive value (PPV) of 100% for both techniques. The sensitivity, negative predictive value (NPV), and diagnostic accuracy for EBUS were 81%, 91%, and 93%, respectively, compared with 79%, 90%, and 93% for mediastinoscopy. Contraindications to EBUS bronchoscopy are similar to routine bronchoscopy in which needle puncture or endobronchial sampling would be anticipated. Complications are rare, with none reported in this series of 153 patients.
Endoscopic Ultrasound and Fine-Needle Aspiration

Traditionally, transesophageal EUS has been performed by trained gastroenterologists and is usually done under conscious sedation. More recently, in Europe and other parts of the world, the EBUS-TBNA scope has been approved for use in the esophagus, allowing chest physicians and surgeons to perform transesophageal EUS. In the mediastinum, EUS can easily assess lymph node stations 2L, 4L (Fig 1A-B), 7, 8R and 8L (right and left paraesophageal, respectively) and 9R and 9L (right and left inferior pulmonary ligament, respectively). Air in the trachea and bronchial tree limits visualization of the right paratracheal lymph node stations, 2R and 4R. Although it is not always safe or feasible to evaluate stations 5 (aortopulmonary window) and 6 (para-aortic), it is possible (Fig 2A-B). Cerfolio et al11 reported on 112 pts with clinically suspected N2 disease where the malignant nodes were located in lymph node station 5 and/or station 6. Implemented in 62 of these 112 patients (56%), EUS-FNA correctly identified N2 disease in 41 patients (66%). Liberman et al12 reported on a novel technique using a long approach through the proximal esophagus of 7 to 8 cm just medial to the left subclavian artery to assess station 6 in 3 patients.

Multiple studies have reported low complications and high success rates. The accuracy of EUS-FNA of the mediastinum has previously been reviewed in a meta-analysis demonstrating a pooled sensitivity of 83% and a specificity of 97%.13 The NPV does not fare as well, at 73% to 83%.6,13 Despite the lower NPV, EUS-FNA avoids the need for surgical staging procedures in 50% to 70% of patients.14

Fig 1A-B. — (A) Endoscopic ultrasound of two station 4L (lower left para-tracheal) lymph nodes (one of which is denoted by crosshairs). (B) Endoscopic ultrasound-guided fine-needle aspiration (arrow) of two station 4L lymph nodes. AO = aorta, PA = pulmonary artery, 4L = station 4L lymph nodes, LN × 2 = two station 4L lymph nodes.

Fig 2A-B. — (A) Positron-emission tomography (PET) scan, coronal view, showing PET-positive aortopulmonary window (station 5) lymph node (arrow) in a patient with recurrent non–small-cell lung cancer after previous left upper lobectomy. (B) Endoscopic ultrasound showing aortopulmonary window lymph node (crosshairs) and left hilar mass in the same patient. AO = aorta, APW = aortopulmonary window, Mass = left hilar mass, PA = pulmonary artery.
The primary tumor can even be aspirated for tissue diagnosis in select situations where the tumor is adjacent to the esophagus. In addition, the celiac axis, the left adrenal gland, and the left lobe of the liver can be potentially evaluated. Mediastinal tumor invasion (T4) can be assessed with sensitivity, specificity, PPV, and NPV rates of 88%, 98%, 70%, and 99%, respectively.7

EUS-guided core biopsies may provide histological information and additional material for immunohistochemistry for specific diagnosis of mediastinal lesions. Also, a core biopsy may facilitate molecular analysis of lung cancer and assess responsiveness to chemotherapeutic agents. Based on two published studies,15,16 it is not clear if EUS-guided core biopsy of thoracic lesions improves the diagnostic accuracy of EUS-FNA, and EUS-guided core biopsy cannot be routinely recommended. However, this technique may be useful in selected patients to confirm histological diagnosis and when additional tissue is required for IHC or molecular analysis.

The ProCore needle (Cook Medical Inc, Bloomington, Indiana) is a relatively new EUS sampling needle designed with a reverse bevel at the tip. This needle is available in different sizes (25g, 22g, and 19g). It enables procurement of core samples and may provide histology. It is technically easy to use and appears to be safe based on the preliminary data. There is no literature on this needle for mediastinal lesions; however, it is likely to provide additional tissue, as shown with pancreaticobiliary masses, and may be used in selected patients.17,18

Factors that previously prevented the widespread adoption of EUS-FNA for NSCLC staging likely included the lack of trained advanced endoscopists, the cost of equipment, the absence of on-site cytopathologists, and the fact that lung cancer is traditionally diagnosed and treated by chest physicians and oncologists. Given the vast increase in advanced endoscopy fellowship programs offering a formal fourth year of gastroenterology training that encompasses EUS, the downstream revenue that usually results from such advanced procedures, and the proven safety and efficacy of a more minimally invasive staging modality, there will likely be greater implementation of EUS-FNA for staging of NSCLC and more definitive formal incorporation of its use in the diagnostic and staging guidelines in the near future.

In addition to downstream revenue, evidence shows that initial EUS-FNA is a cost-effective approach. Sharples et al19 published a prospective, international, open-label, randomized controlled study with a trial-based economic analysis to assess the cost-effectiveness of EUS-FNA (followed by surgical staging if EUS-FNA was negative) compared with standard surgical staging alone in patients with NSCLC and who were otherwise candidates for surgery. Sensitivity for detecting N2/N3 metastases was 79% (41/52; 95% confidence interval [CI], 66%–88%) for the surgical arm compared with 94% (62/66; 95% CI, 85%–98%) for the EUS-FNA arm (P = .02). Unnecessary thoracotomies occurred in 18% of patients in the surgical arm and in 7% in the EUS-FNA arm (P = .02).

### Endoscopic Ultrasound and Endobronchial Ultrasound Combined

The combination of EBUS with EUS allows for tissue sampling and more definitive differentiation of lymph nodes by the use of both transbronchial and transesophageal FNA. Transesophageal EUS may be combined with EBUS to access lymph node stations that are inaccessible by EBUS and allows near complete mediastinal staging. The risk of undergoing combined EBUS and EUS is simply the sum of the risk of EBUS and the risk of EUS when performed separately.

In 2008, Wallace et al20 investigated the diagnostic accuracy of routine TBNA, EBUS-FNA, and EUS-FNA without the use of rapid on-site cytological examination in 138 patients with a known or suspected thoracic malignancy. Investigators were blinded to the results of each other’s procedures, and the diagnostic standard for patients for a negative minimally invasive workup was mediastinoscopy, thoracoscopy, or open surgical procedure showing no disease or 6 to 12 months of follow-up without evidence of lymph node enlargement. Their findings suggested that EBUS-FNA had a higher sensitivity (with the exception of lymph node station 7, or subcarinal lymph nodes, which were equivalent) compared to routine TBNA, and also that EUS plus EBUS may allow near complete minimally invasive staging of this patient population. The sensitivity for this combined approach was 93%, with an NPV of 97% and specificities and PPV of 100%.

Herth et al21 have shown that both EUS-FNA and EBUSTBNA can be performed at the same session by a single operator using the same endobronchial echoendoscope, and the sensitivity and specificity of the techniques when combined are higher than those of each one used separately. Although cost was not addressed in this study, performing both procedures at the same session by one operator would most likely result in cost savings, improved efficiency, and superior yield. Endoscopic biopsies were done on 619 lymph nodes from 139 patients diagnosed with NSCLC: 229 by EUS-FNA and 390 by EBUS-TBNA. Sensitivity was 89% for EUS-FNA and 92% for EBUS-TBNA. The combined approach had a sensitivity of 96% and an NPV of 95%, which were higher values than those for either approach alone. The authors concluded that the two endoscopic procedures can easily be performed with a dedicated linear EBUS bronchoscope in one setting and by one operator.
and that the two endoscopic approaches are complementary and provide better diagnostic accuracy than either one alone.

As additional evidence that the two endoscopic approaches complement each other, EUS-FNA and EBUS-TBNA were compared in 33 patients for the staging of lung cancer or for diagnosis of a suspicious mediastinal lesion in patients with suspected lung cancer. Each endoscopic technique was unsuccessful in 1 patient. A total of 119 lesions were sampled by EUS-FNA (n = 59) and EBUS-TBNA (n = 60). EUS-FNA and EBUS-TBNA demonstrated cancer in 26 and 28 lesions, respectively, and benign cytology in 30 and 28 lesions, respectively. When the 60 EBUS-TBNA samples were compared with the 59 EUS-FNA samples, 11 additional cancer diagnoses and 3 samples with suspicious cells were obtained by EBUS-TBNA that had not been obtained by EUS-FNA. Conversely, EUS-FNA diagnosed 12 additional cancer diagnoses, 1 suspicious and 1 specific benign diagnosis (sarcoidosis) in addition to those by EBUS-TBNA. The accuracy of EUS-FNA and EBUS-TBNA, in combination, for the diagnosis of mediastinal cancer was 100% (95% CI, 83%-100%). The authors concluded that EUS-FNA and EBUS-TBNA appeared to be complementary and that a combined approach with both EUS-FNA and EBUS-TBNA might be able to replace more invasive methods for evaluating not only lung cancer but also unclear mediastinal or hilar lesions.

Zhang et al recently reported the estimated summary measures for quantitative analysis of EBUS-TBNA plus EUS-FNA for mediastinal nodal staging of lung cancer: sensitivity of 86% (95% CI, 82%-90%), specificity of 100% (95% CI, 99%-100%), positive likelihood ratio of 51.8 (95% CI, 22.5-118.9), negative likelihood ratio of 0.15 (95% CI, 0.09-0.25), diagnostic odds ratio of 416.8 (95% CI, 140.1-1240.5), and area under the curve (AUC) of 0.99. The authors concluded that, based on this recent meta-analysis of 8 studies that evaluated both endoscopic techniques (EUS and EBUS), the diagnostic power of this combined technique is accurate and has a higher sensitivity and specificity than each done alone and that, as an almost minimally invasive examination, EUS-FNA plus EBUS-TBNA might replace more invasive methods for evaluating mediastinal node staging of lung cancer.

In addition, Ohnishi et al published a prospective study on a consecutive series of 120 patients who had resectable suspected lung cancers on CT scan findings and who underwent PET-CT scan and combined EUS-FNA plus EBUS-TBNA. The accuracy of the combined approach using EUS-FNA plus EBUS-TBNA was significantly higher than that of PET-CT alone (90.0% vs 73.6%; P < .0001). The sensitivity, specificity, PPV, and NPV were 71.8%, 100%, 100%, and 86.6%, respectively, for the combined approach vs 47.4%, 87.5%, 66.7%, and 75.9%, respectively, for PET-CT alone. Since the combined endoscopic approach using EUS-FNA and EBUS-TBNA provided excellent diagnostic performance, the authors recommended EUS-FNA plus EBUS-TBNA before surgery or mediastinoscopy in order to avoid futile thoracotomy and surgical intervention.

Based on a review of these and similar studies, the 2011 clinical guidelines from the National Institute of Health and Clinical Excellence recommend the combination of EUS-FNA and EBUS-TBNA as an alternative to surgical staging.

Conclusions
Minimally invasive staging of the mediastinum in patients with known or suspected non–small-cell lung cancer may be readily performed by trained experienced endoscopists, with studies suggesting results similar to mediastinoscopy in experienced hands. Although the current literature suggests equivalent results, at this point in time standard of care would dictate invasive staging at the time of surgery in surgically fit patients. Current barriers to the dissemination of these techniques include initial cost of equipment, lack of access to rapid on-site cytology, and the time required to obtain sufficient skills to duplicate published results. Hospitals and health care systems, which may be reluctant to absorb initial set-up costs, could evaluate downstream revenue as justification for expanding these technologies, as described in published models.

References


