Endobronchial ultrasonography (EBUS)—Its role in staging of non–small cell lung cancer and who should do it?

Rafael S. Andrade, MD, David D. Odell, MD, MMSc, Jonathan D’Cunha, MD, PhD, and Michael A. Maddaus, MD

Endobronchial ultrasonography with transbronchial needle aspiration biopsy (EBUS-TBNA) has gained acceptance as an alternative to mediastinoscopy to diagnose and stage non–small cell lung cancer (NSCLC).^{1,2} Once a decision has been made to obtain biopsy specimens of mediastinal lymph nodes (MLNs), the choice of biopsy technique gains importance. However, despite the extensive experience with EBUS-TBNA in many centers, one must keep in mind that the Achilles’ heel of EBUS-TBNA is the greater variability in negative predictive value (NPV) compared with mediastinoscopy (EBUS-TBNA NPV = 60%-99%; mediastinoscopy NPV = 80%-99%), generating an increased concern for false negative results. Because false negative findings can have a major detrimental impact on patient outcomes, the physician performing EBUS-TBNA must use the best single procedure or combination of techniques to ensure the most accurate results of mediastinal staging.

WHAT IS THE ROLE OF EBUS-TBNA IN STAGING NSCLC?

Once a decision has been made to pathologically stage the mediastinum in a patient with suspected or confirmed NSCLC, the role of EBUS-TBNA will be determined by a variety of factors. The diagnostic performance of the test will depend on the pretest probability of N2 disease, physician skills, quality and evaluation skills of the sample by a cytopathologist, and the clinician’s interpretation of the results.

Pretest Probability

Inasmuch as not all patients with NSCLC will have the same probability of positive N2 MLNs, the implications of an imperfect NPV are variable. The main concern for clinicians is the possibility of understaging a patient’s disease with a false negative, which could result in

suboptimal treatment. In patients with a low pretest probability of N2 disease, the likelihood of a false negative result is low. In general, in these patients a negative result is sufficiently reliable to guide further treatment decisions. However, if a patient’s probability of N2 disease is higher, as in a patient with a large and/or centrally located tumor, then the less than optimal NPV may warrant much greater caution in clinical decision making. We have designed a schematic for the role of EBUS-TBNA in NSCLC staging based on pretest probability (Figures 1 and 2). Scans are shown in Figures 1, B and C and Figures 2, B and C.

Physician EBUS Skills

Physician EBUS skills are determined by an individual’s technical skills and by his or her level of understanding of the impact of an inaccurate MLN biopsy on the outcome of a patient with NSCLC. It is essential to realize that published results on EBUS-TBNA as a staging tool in NSCLC mainly come from expert centers and are not likely to be reproducible in less experienced centers.

Technical skills. The American College of Chest Physicians³ recommends that 50 EBUS procedures be required to prove proficiency. Although the technical skills required for identifying and sampling enlarged MLNs are quite basic, proficiency in identifying normal-sized MLNs in all relevant MLN stations requires significantly more experience and commitment to technical perfection. Much as with mediastinoscopy, a physician performing EBUS must sample all relevant MLN stations even if MLNs have benign ultrasonographic appearance. Ideally, we recommend that physicians performing EBUS also seek to achieve proficiency in esophageal endoscopic ultrasound because the combination of esophageal endoscopic ultrasound and EBUS has a higher diagnostic yield than either procedure alone.⁴

Understanding of NSCLC. In our opinion, for a physician to be fully qualified to perform EBUS in a patient with NSCLC, the physician must function as part of a multidisciplinary lung cancer team. Additionally, the physician needs to be completely familiar with each patient’s clinical presentation because patient-specific factors may influence the mediastinal staging algorithm. Finally, the physician must have experience with management of patients with

From the Section of Thoracic and Foregut Surgery, Department of Surgery, University of Minnesota, Minneapolis, Minn.

Disclosures: Authors have nothing to disclose with regard to commercial support. Presented at the 3rd International Minimally Invasive Thoracic Surgery Summit, Boston, Massachusetts, October 7-8, 2011.

Address for reprints: Rafael S. Andrade, MD, Section of Thoracic and Foregut Surgery, Department of Surgery, University of Minnesota, MMC 207, 420 Delaware St SE, Minneapolis, MN 55455 (E-mail: andr0119@umn.edu).

J Thorac Cardiovasc Surg 2012;144:S9-13

0022-5223/\$36.00

Copyright © 2012 Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2012.03.068

Abbreviations and Acronyms

EBUS	= endobronchial ultrasonography
MLN	= mediastinal lymph node
NPV	= negative predictive value
NSCLC	= non-small cell lung cancer
ROSE	= rapid on-site evaluation
TBNA	= transbronchial needle aspiration biopsy

NSCLC to provide the skill and judgment for interpretation of results and risk stratification.

Quality and Evaluation of the Sample

The clinical applicability and precision of EBUS-TBNA as a diagnostic tool in NSCLC depends to a great extent on the quality of the sample and on the cytopathologist's skills.⁵ The role of the cytopathologist is just as important as the role of the EBUS-TBNA operator.

Quality of the sample. A minimum requirement of cellularity is indispensable to permit cytopathologic interpretation of an EBUS-TBNA sample.⁶ The presence of 40 lymphocytes per high-power field in the more cellular areas of the smear and/or the presence of clusters of pigmented macrophages are good predictors of the adequacy of a sampled lymph node free of metastasis. In certain cases of nodal replacement by granulomatous disease, lymphoid tissue might not be seen in samples that remain satisfactory for evaluation.

Evaluation of the sample. At our institution, an experienced cytopathologist is always available for rapid on-site evaluation (ROSE) of samples. We believe real-time communication between the operator and the cytopathologist is crucial to maximize the yield of the procedure. The cytopathologist can inform the operator within a few minutes whether a specimen is adequately cellular (see above) or nondiagnostic (eg, mainly blood or bronchial cells). An adequate sample will then be classified as (1) benign lymphocytes, (2) benign pathology (eg, granuloma), or (3) malignant pathology. The concordance between ROSE and final cytologic analysis at our institution is 95%.⁷ However, in our experience of more than 400 EBUS-TBNA procedures, about 15% of MLN samples continue to be nondiagnostic.⁶

If ROSE is not available at an institution, then the EBUS physician cannot make an intraprocedural decision regarding the adequacy of sampling. However, if the physician has a consistent technique, ROSE will probably not have a significant impact on overall test performance. The role of ROSE in EBUS-TBNA is to facilitate early decision making. Although ROSE affects the timing of the decision, its availability does not affect the decision itself.

Clinician's Interpretation of the Results and Decision Making

The interpretation of EBUS-TBNA results requires the clinician's comprehension of the limitations of the test. To clearly understand the reliability of EBUS-TBNA in mediastinal staging in NSCLC, the clinician must understand the importance of the NPV and how NPV should be determined.

Calculation of the NPV of EBUS-TBNA. The NPV is the most important measure of test performance for EBUS-TBNA in patients with lung cancer. The calculation represents the percentage of patients who will have a negative test result in the presence of actual disease (*false negatives*). Such false negative results can lead to understaging and suboptimal therapy. We herein review the calculation of NPV to underscore its importance.

The definition of NPV is as follows:

$$\text{NPV} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}}$$

However, when applied to EBUS-TBNA in NSCLC staging, this definition does not factor in nondiagnostic samples. Inasmuch as clinicians cannot make treatment decisions on the basis of nondiagnostic samples, these findings should probably be added to the NPV denominator.

Our conservative NPV calculation for EBUS-TBNA is as follows:

$$\text{NPV} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives} + \text{Nondiagnosics}}$$

Additionally, this calculation does not take into consideration the pretest probability of N2 disease. The relevance of a negative or nondiagnostic sample varies with the pretest probability of N2 disease; we believe that the "true" NPV is probably somewhere between these 2 calculations. We also suggest that NPV be calculated on a per-patient basis instead of on a per-MLN basis, because decisions are made on patients rather than on individual MLN stations.

How should the clinician decide if the EBUS-TBNA result is trustworthy? Our proposed algorithm takes into consideration the pretest probability of N2 disease as well as the *true* NPV. This algorithm may help guide clinicians in the safe application of EBUS-TBNA evaluation of patients with NSCLC. In our opinion, EBUS-TBNA can accurately and minimally invasively stage up to 85% of appropriately selected patients with NSCLC.

WHO SHOULD DO IT?

The EBUS-TBNA operator—either a thoracic surgeon or an interventional pulmonologist—should be an active member of a multidisciplinary lung cancer care team.

A

B

C

FIGURE 1. A, Algorithm for the use of endobronchial ultrasonography with transbronchial needle aspiration biopsy (EBUS-TBNA) as a staging modality in patients with non-small cell lung cancer (NSCLC) based on pretest probability of disease by imaging. Diagnostic approach in patients with normal computed tomographic (CT) imaging stratified by high (Figure 1, B) and low (Figure 1, C) probability of disease. B, High-probability normal computed tomographic (CT) scan. CT scan and matching positron emission tomographic/computed tomographic (PET-CT) scan images of a patient with a centrally located, intensely PET-positive right upper lobe adenocarcinoma and a radiologically normal mediastinum. In such a patient, a cytologically adequate endobronchial ultrasonogram with a transbronchial needle aspiration biopsy (EBUS-TBNA) sample that is negative for cancer should be verified with surgical biopsy. C, Low-probability normal computed tomographic (CT) scan. CT scan of a patient with a less than 2-cm left upper lobe non-small cell lung cancer (NSCLC) and normal-appearing mediastinal lymph nodes in 4L. Inasmuch as the probability of N2 disease is low, a cytologically adequate endobronchial ultrasonography with transbronchial needle aspiration biopsy (EBUS-TBNA) that is negative for malignancy can be accepted with minimal concern for a false negative result.

Designation of the appropriate provider will vary with local institutional culture and physician availability. However, the institutional practice should be in line with the purpose of the multidisciplinary lung cancer care team: to optimize patient care and properly allocate resources.

Optimization of Patient Care

The optimization of NSCLC treatment is a matter of providing timely and streamlined patient care.⁸ Because

EBUS-TBNA is generally performed in the initial stages of the evaluation of a patient with NSCLC, the timeliness of EBUS-TBNA sets the stage for subsequent therapy. When ROSE is available, patients can be divided into 2 basic groups: patients who are likely to need solely EBUS-TBNA and no other procedure and patients who are likely to require an additional procedure pending the immediate (ROSE) results of EBUS-TBNA. In the latter group, any additional diagnostic or therapeutic procedures (eg,

FIGURE 2. A, Approach to patients with abnormal computed tomographic/positron emission tomographic (CT/PET) imaging and either high (Figure 2, B) or low (Figure 2, C) probability of malignancy. B, High-probability abnormal computed tomographic (CT) scan. CT scan and matching positron emission tomographic/computed tomographic (PET-CT) scan images of a patient with cytologically confirmed N2 metastases in stations 4R and 7, but endobronchial ultrasonography with transbronchial needle aspiration biopsy (EBUS-TBNA) samples from 4L revealed normal lymphocytes. A surgical biopsy is recommended to confirm that 4L is indeed negative. C, Low-probability abnormal computed tomographic (CT) scan. CT scan and matching positron emission tomographic/computed tomographic (PET-CT) scan images of a patient with a mildly PET-positive left upper lobe non-small cell lung cancer (NSCLC) and diffusely enlarged, partially calcified, PET-positive mediastinal lymph nodes (MLNs) that also involve the opposite hilum. In this patient the mediastinal findings could be explained by granulomatous disease; an endobronchial ultrasonogram with transbronchial needle aspiration biopsy (EBUS-TBNA) sample that demonstrates granulomatous disease would be trustworthy. However, samples with only normal lymphocytes or nondiagnostic samples should prompt the operator to pursue a surgical biopsy.

surgical MLN biopsy, lung resection, placement of vascular access for chemotherapy) can be performed in the same anesthetic setting to further streamline patient care. In our experience, roughly 50% of patients who undergo EBUS-TBNA have an additional procedure performed in the same setting.⁷

Resource Allocation

Resource allocation is a key factor in the proper delivery of health care. Although we do not have data directly comparing the cost of performing EBUS-TBNA in the operating room versus in the bronchoscopy suite (regardless of type of anesthesia), performing EBUS-TBNA in the bronchoscopy

suite probably consumes less time and personnel (and hence is less costly) than in the operating room. As a stand-alone procedure, EBUS-TBNA would be best performed in the bronchoscopy suite. However, if ROSE is available and the patient is likely to require an additional procedure on the basis of immediate results of EBUS-TBNA, then performing EBUS-TBNA in the operating room could be logistically and financially prudent.

Who Should Do It?

So long as the person who performs EBUS-TBNA is a member of the multidisciplinary lung cancer care team, has a thorough understanding of NSCLC, and is familiar with the individual patient's clinical situation, the issue of thoracic surgeon versus interventional pulmonologist as operator is irrelevant. The primary advantage of a thoracic surgeon performing EBUS as a staging procedure is the ability to perform any other procedure if necessary at the same setting, whether diagnostic or therapeutic.

In our opinion, if EBUS-TBNA is performed in the bronchoscopy suite as a stand-alone procedure, the interventional pulmonologist would be the preferred operator. However, if EBUS-TBNA is performed on a patient who is likely to require an additional procedure, it should ideally be performed by the thoracic surgeon in the operating theater.

CONCLUSIONS

When performed by committed and well-trained physicians, EBUS-TBNA can accurately and minimally

invasively stage the mediastinum in up to 85% of appropriately selected patients with NSCLC. The EBUS physician, regardless of specialty, must be a member of the multidisciplinary lung cancer care team, must have a thorough understanding of NSCLC, and must be familiar with the individual patient's clinical situation.

References

1. Groth SS, Andrade RS. Endobronchial and endoscopic ultrasound-guided fine-needle aspiration: a must for thoracic surgeons. *Ann Thorac Surg*. 2010;89:S2079-83.
2. Yasufuku K, Pierre A, Darling G, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg*. 2011;142:1393-400.
3. Ernst A, Silvestri GA, Johnstone D. Interventional pulmonary procedures: guidelines from the American College of Chest Physicians. *Chest*. 2003;123:1693-717.
4. Szlubowski A, Zieliński M, Soja J, Annema JT, Sośnicki W, Jakubiak M, et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging—a prospective trial. *Eur J Cardiothorac Surg*. 2010;37:1175-9.
5. Cameron SE, Andrade RS, Pambuccian SE. Endobronchial ultrasound-guided transbronchial needle aspiration cytology: a state of the art review. *Cytopathology*. 2010;21:6-26.
6. Alsharif M, Andrade RS, Groth SS, Stelow EB, Pambuccian SE. Endobronchial ultrasound-guided transbronchial fine-needle aspiration: the University of Minnesota experience, with emphasis on usefulness, adequacy assessment, and diagnostic difficulties. *Am J Clin Pathol*. 2008;130:434-43.
7. Andrade RS, Groth SS, Rueth NM, D'Cunha J, Pambuccian SE, Maddaus MA. Evaluation of mediastinal lymph nodes with endobronchial ultrasound: the thoracic surgeon's perspective. *J Thorac Cardiovasc Surg*. 2010;139:578-82; discussion 582-3.
8. Coory M, Gkolias P, Yang IA, Bowman RV, Fong KM. Systematic review of multidisciplinary teams in the management of lung cancer. *Lung Cancer*. 2008;60:14-21.