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Original Research

INTERVENTIONAL PULMONOLOGY

Combined Endoscopic-Endobronchial Ultrasound-Guided Fine-Needle Aspiration of Mediastinal Lymph Nodes Through a Single Bronchoscope in 150 Patients With Suspected Lung Cancer

Felix J. F. Herth, MD, FCCP; Mark Krasnik, MD; Nicolas Kahn, MD; Ralf Eberhardt, MD; and Armin Ernst, MD, FCCP

Background: **For mediastinal lymph nodes, biopsies must often be performed to accurately stage lung cancer. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) allows real-time guidance in sampling paratracheal, subcarinal, and hilar lymph nodes, and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can sample mediastinal lymph nodes located adjacent to the esophagus. Nodes can be sampled and staged more completely by combining these procedures, but to date use of two different endoscopes has been required. We examined whether both procedures could be performed with a single endobronchial ultrasound bronchoscope.**

Methods: **Consecutive patients with a presumptive diagnosis of non-small cell lung cancer (NSCLC) underwent endoscopic staging by EBUS-TBNA and EUS-FNA through a single linear ultrasound bronchoscope. Surgical confirmation and clinical follow-up was used as the reference standard.**

Results: **Among 150 evaluated patients, 139 (91%; 83 men, 56 women; mean age 57.6 years) were diagnosed with NSCLC. In these 139 patients, 619 nodes were endoscopically biopsied: 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 a negative predictive value of 95%, values higher than either approach alone. No complications occurred.**

Conclusions: **The two procedures can easily be performed with a dedicated linear endobronchial ultrasound bronchoscope in one setting and by one operator. They are complementary and provide better diagnostic accuracy than either one alone. The combination may be able to replace more invasive methods as a primary staging method for patients with lung cancer.**

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Abbreviations: EBUS = endobronchial ultrasound; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; EUS = endoscopic ultrasound; EUS-FNA = endoscopic ultrasound-guided fine-needle aspiration; TBNA = transbronchial needle aspiration

Lung cancer is one of the most common neoplasms in the Western world. Treatment depends on histologic type and stage of disease.[1] Mediastinal lymph nodes are involved in 28% to 38% of non-small cell lung cancers at the time of diagnosis, and when present, they have an important bearing on treatment planning.[2] Professional societies recommend staging with tissue confirmation of suspected metastatic mediastinal lymph nodes.[1,2] Mediastinoscopy or thoracoscopy has been the diagnostic standard, but less-invasive methods have emerged as potential alternatives.[3] Such methods include conventional transbronchial needle aspiration (TBNA), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and most recently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).[4-7]

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Conventional TBNA does not allow needle placement to be visualized; it is a fairly "blind" technique.

Also, failure to place the needle directly into the node is the leading cause of a lower biopsy yield. Real-time guidance of needle punctures addresses this problem[8,9] and offers substantial advantages in sampling mediastinal nodes.[10,11] Endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS) also detect mediastinal lymph nodes as small as 3×5 mm to allow for reliable ultrasound-guided fine-needle aspiration of the radiologically normal mediastinum.[12,13]

Several studies have found that combining EBUS-TBNA and EUS-FNA in a single procedure has a higher staging accuracy than either procedure alone in patients with suspected lung cancer.[14-17] However, studies to date have used both an EBUS bronchoscope and an EUS endoscope, necessitating the purchase and maintenance of expensive equipment and training in the use of different endoscopes. To simplify this promising approach, we sought to determine whether both procedures could be performed through a single bronchoscope in the same setting by the same operator.

Materials and Methods

The study was approved by the local institutional review boards, and procedures were performed by all authors. All patients provided written informed consent to the procedure. Consecutive patients seen between January 2004 and December 2006 were included in the study if they had enlarged lymph nodes and known or suspected non-small cell lung cancer and no evidence of extrathoracic metastases. Before the endoscopy, all patients underwent a CT scan with contrast of the chest. A PET scan was performed on an individual basis as required. Lymph nodes were considered to be enlarged if the short-axis diameter was ≥ 1 cm as measured on the CT scan.

Endoscopy and Biopsy Procedures

Both procedures were performed with a flexible linear ultrasound bronchoscope (UF Olympus Medical; Tokyo, Japan) as an outpatient procedure. The ultrasound transducer scans parallel to the insertion direction of the bronchoscope and is connected to a dedicated ultrasound scanner (EU-C60; UF Olympus Medical, or Prosound α 5; Aloka, Japan), with Doppler-flow imaging to detect blood vessels.

With the patient receiving moderate sedation or general anesthesia, we first performed EBUS-TBNA in standard fashion. This was followed by EUS-FNA in the same session. For this purpose, the bronchoscope was introduced through the mouth and advanced from the left to the pharynx into the esophagus under gentle pressure. Patients under moderate sedation were asked to swallow in order to assist in advancing the instrument. Inflation was not performed. Continuous ultrasound imaging was employed to assess proper location (Fig 1). The left adrenal gland and the left liver lobe were not examined because of the length of the EBUS-TBNA scope.

When a lesion was located, the needle was introduced through the biopsy channel of the endoscope. A power Doppler examination was carried out immediately before the biopsy to prevent unintended puncture of vessels. The needle was placed in the lesion under real-time ultrasonic guidance, and the stylet was then removed. Suction was applied with a syringe, and the needle was moved back and forth inside the lesion. The specimen was expelled onto glass slides and smeared, air dried, and stained for cytologic examination. A cytopathologist was not present during the examination, and rapid on-site cytopathologic examination was not performed.

The endoscopic tissue diagnosis was confirmed by open thoracotomy, thoracoscopy, or clinical follow-up over 6 to 12 months.

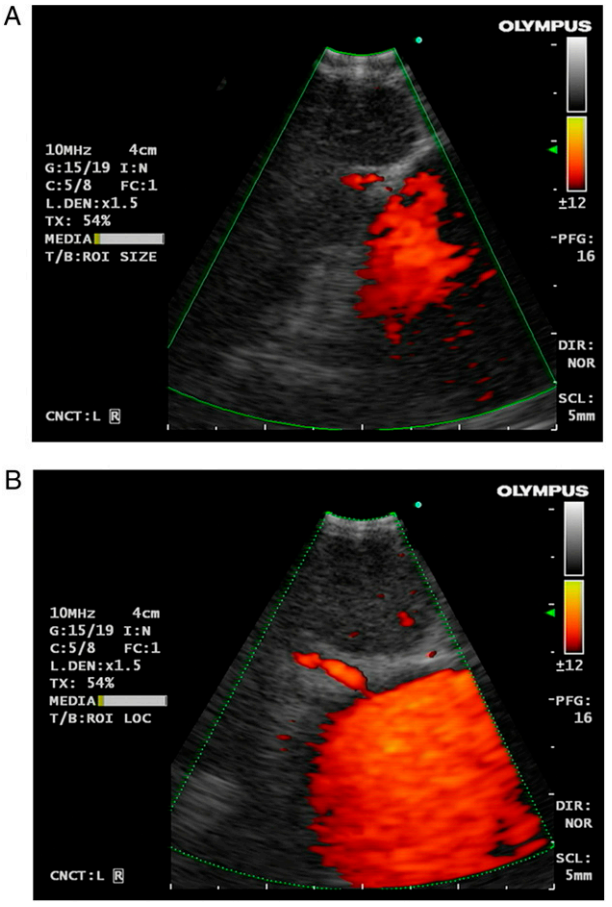

Figure 1. Image of an enlarged lymph node in the position 4l with the endobronchial ultrasound (EBUS) scope from the endobronchial view (*A*) and the endoesophageal view (*B*). Orange areas show Doppler flow in a vessel.

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A positive cytologic result of malignancy was accepted as evidence of cancer, and the patients were treated accordingly.

Statistical Methods

Diagnostic sensitivity, specificity, and accuracy were calculated using the standard definitions, and α was set at 0.05. The SPSS 11.5 statistical software package (SPSS Inc; Chicago, IL) was used for all analyses.

Results

The procedure was completed without complication in all 150 eligible patients. Of these, 139 (91%; 83 men, 56 women; mean age 57.6 years) had non-small cell lung cancer and were included in the analysis. Of the 11 excluded patients, three had extrathoracic malignant disease, three had small cell lung cancer, two had sarcoidosis, two refused surgery to establish a diagnosis, and one had cryptogenic organizing pneumonia.

We sampled 619 nodes, 229 with EUS-FNA and 390 with EBUS-TBNA (Table 1). Sampled nodes were adjacent to the trachea and main bronchi at stations 2, 4, 7, 10, and 11 and from the posterinferior bronchi at stations 4l, 7, 8, and 9 (Table 2). The mean number of lymph nodes sampled with EUS-FNA and EBUS-TBNA per patient was 1.7 and 2.8, respectively. Sampled nodes ranged from 8 to 22 mm (mean 17 mm; SD 4.2 mm). The mean procedure time for the EBUS-TBNA was 14 min and for the EUS-FNA, 16 min.

Out of 139 patients, 71 (52%) proved to have malignant mediastinal disease. EBUS-TBNA was able to detect the malignant nodes in 65 patients (91%) and EUS-FNA in 63 patients (89%). The combined technique had the highest detection rate: In 68 patients (96%) the malignant nodes were detected (Table 1).

EBUS-TBNA was more sensitive than EUS-FNA (92% vs 89%) (Table 2). The combination of EUS-FNA and EBUS-TBNA had the highest estimated sensitivity (96%) and negative predictive value (96%) compared with either method alone (Table 3).

Sixty-eight patients proved to have no evidence for malignant lymph node involvement as confirmed by surgical biopsy or clinical follow-up. None of these patients had a positive endoscopic biopsy. Three patients did not have diagnostic tissue or lymphocytes in the specimen. One of these patients proved to have malignant lymph node involvement on surgery (Fig 2).

All patients tolerated the combined procedures well, and a complete examination was possible in all cases. No procedure had to be terminated early as a result of patient intolerance, and there were no periprocedural complications.

Discussion

Cytologic or histologic evaluation of mediastinal and thoracic lymph nodes in lung cancer is essential to stage the disease accurately and to plan treatment. Mediastinoscopy, a surgical procedure requiring general anesthesia, is the current diagnostic standard for staging mediastinal lymph nodes, having a negative predictive value of 89% and a positive predictive value of 100%, but it has limitations. Mediastinoscopy is best suited for sampling lymph nodes in the pretracheal and paratracheal regions, but it is limited in accessing the inferior and posterior mediastinum and the aortopulmonary window. Although generally safe, mediastinoscopy has a 2% risk of major morbidity, a 0.08% risk of mortality, and is costly because of its significant resource use (eg, operating room time).

EBUS-TBNA and EUS-FNA have emerged as alternatives for primary mediastinal staging because of their high diagnostic yield, access to nodes beyond the reach of the mediastinoscope, and low morbidity.[1,2] Both procedures can be performed with the use of moderate sedation in regular procedure rooms on an outpatient basis. EBUS-TBNA has been shown to have excellent sensitivity and positive predictive value in lung cancer staging[5,8,18-22] and, besides mediastinal stations, can access hilar lymph nodes as well in the same setting. EUS-FNA has had very comparable results and, besides mediastinal nodes, can access sites of periesophageal disease, such as stations 8 and 9. In fact, both endoscopic technologies have been shown in randomized trials[23,24] to be individually superior to mediastinoscopy.

Increasingly, EUS-FNA and EBUS-TBNA are thought of as complementary rather than competitive

Table 1—*Diagnostic Performance Characteristics of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration and Endoscopic Ultrasound-Guided Fine-Needle Aspiration in 619 Nodes From 139 Patients With Suspected Cancer*

Sampling Approach	Nodes Sampled, No. (%)	Sensitivity for Cancer Detection, %	Specificity for Cancer Detection, %	Negative Predictive Value, %
Esophageal	229 (37)	89	100	82
Endobronchial	390 (63)	91	100	92
Combined	619 (100)	96	100	96

Table 2—*Number of Patients Undergoing Lymph Node Punctures per Specific Station*

Lymph Node Station	Ultrasound Technique		
	EBUS	EUS	EBUS + EUS
2R	11	2	2
2l	8	13	8
4r	27	13	13
4l	22	21	21
7	34	34	34
10r	23	12	12
10l	14	13	13
8	0	28	0
9	0	15	0
N	139	139	103

EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound.

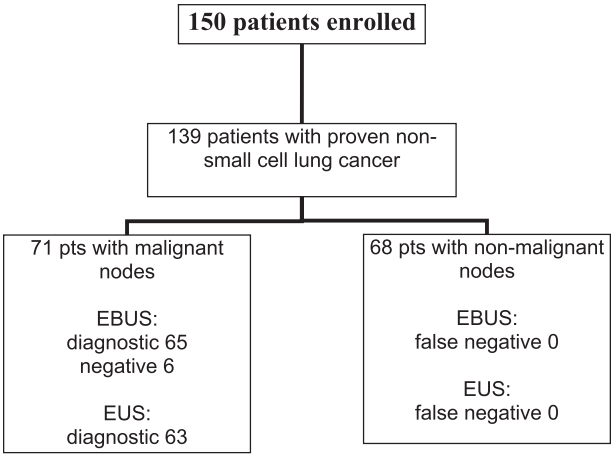

FIGURE 2. Flow diagram of patients enrolled in the study and procedures performed. EUS = endoscopic ultrasound; pts = patients. See Figure 1 legend for expansion of other abbreviation.

procedures. The combined reach to mediastinal, hilar, and periesophageal disease would afford the most complete staging possible.

Vilmann et al[14] studied 33 patients, in which 119 lesions were sampled by EUS-FNA and EBUS-TBNA. The results for EUS-FNA vs EBUS-TBNA for diagnosing mediastinal cancer were: sensitivity, 80% vs 85%; specificity, 100% vs 100%; negative predictive value, 66% vs 72%; and accuracy, 86% vs 89%, respectively. The diagnostic accuracy of the combined approach was 100%. Wallace et al[15] used the combined approach in 138 patients and found similar results for each technique (sensitivity, 69%). The combined approach also had higher sensitivity (93%) and a higher negative predictive value (97%) for detecting lymph nodes in any mediastinal location. Thus, the combined approach appears to be more useful than is either alone.

Logistically, it would be most desirable to perform both procedures in the same setting because it would save patients a second procedure day and would maximize resource use. Practically, though, there are significant problems: To date, combining EUS-FNA and EBUS-TBNA requires the use of two different and expensive systems. Also, additional training is required, and as a matter of fact, few bronchoscopists are skilled in the use of an EUS endoscope. We therefore think that our study provides a potential solution to this problem. The use of one scope for both applications addresses the equipment issue and alleviates technical training hurdles. If one person can perform the procedure, it also makes scheduling easier because getting two skilled endoscopists together is at times difficult to arrange.

In this study, we show that the use of a single scope is feasible and safe as well as very effective. It enables near complete thoracic lymph node staging by one operator and in one setting. In experienced hands, this may well develop as the preferred initial staging technology in lung cancer.

Some shortcomings of this approach deserve mention, though. It still cannot access some lymph node stations. Station 3, and especially the aortopulmonary window, remain out of reach. Also, conventional EUS-FNA can reach extrathoracic sites of disease such as the left adrenal area, which is not accessible with our approach because the bronchoscope is too short. A solution to be considered is the development of a dedicated "staging ultrasound-endoscope" that would add some length and incorporate some other minor design changes.

All procedures in this study were performed by bronchoscopists experienced in EBUS aspiration. Given the range of operator variability, the expected success rate under other circumstances is unclear, and the specific training and credentialing requirements for combined procedures such as described in this article would need to be established. The fact that other specialties such as cardiology and anesthesiology have shown the use of transesophageal ultrasound imaging to be safe and effective is important to consider.

Table 3—*Number of Patients Who Underwent Esophageal Punctures, Endobronchial Punctures, and Both Procedures of Specific Lymph Node Stations*

Lymph Node Station	Ultrasound Technique		
	EBUS + EUS	EBUS Correct	EUS Correct
2R	2	2/2	1/2
2l	8	7/8	8/8
4r	13	12/13	10/13
4l	21	20/21	20/21
7	34	33/34	34/34
10r	12	12/12	9/12
10l	13	12/13	13/13

See Table 2 for expansion of abbreviations.

Conclusions

Combining esophageal and bronchoscopic endoscopic staging with a single, dedicated linear ultrasound bronchoscope in a single setting performed by an experienced endoscopist is feasible, safe, and effective. The results are excellent, and future studies may support that this approach could be the primary staging procedure for patients with lung cancer.

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Author contributions: All authors had full access to the data.
Dr Herth: participated in the design of the study, performed procedures, and prepared the manuscript.
Dr Krasnik: participated in the design of the study and performed procedures.
Dr Kahn: participated in the design of the study and performed procedures.
Dr Eberhardt: participated in the design of the study and performed procedures.
Dr Ernst: participated in the design of the study, performed procedures, and prepared the manuscript.
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