

# Minimally Invasive Endoscopic Staging of Suspected Lung Cancer

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LUNG CANCER IS THE MOST COMMON cancer-related cause of death in the United States.<sup>1</sup> Stage of disease dictates the choice of therapy. Surgery is most appropriate for patients in whom disease is confined to the lung and hilar lymph nodes. For patients with ipsilateral mediastinal lymph node metastases, the benefit of surgery as primary therapy is questionable. For patients with contralateral mediastinal lymph node metastases, surgery is generally not indicated, and chemotherapy, radiotherapy, or both are considered the standard of care.<sup>2</sup>

Noninvasive staging with chest computed tomography (CT) or positron emission tomography (PET) is associated with high rates of false-positive and false-negative results, respectively.<sup>3</sup> The American College of Chest Physicians recommends invasive staging with tissue confirmation of suspected metastatic mediastinal lymph nodes.<sup>4</sup> Mediastinoscopy or thoracoscopy has been the diagnostic standard, but less invasive methods have emerged as poten-

**Context** In patients with suspected lung cancer, the presence of mediastinal lymph node metastasis is a critical determinant of therapy and prognosis. Invasive staging with pathologic confirmation is recommended. Many methods for staging exist; mediastinoscopy, an invasive procedure requiring general anesthesia, is currently regarded as the diagnostic standard.

**Objective** To compare the diagnostic accuracy of 3 methods of minimally invasive endoscopic staging (and their combinations): traditional transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA), and transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). In particular, we aimed to compare EBUS-FNA with TBNA.

**Design, Setting, and Participants** Invasive staging of the mediastinum among consecutive patients with suspected lung cancer at a US academic medical center from November 2004 through October 2006.

**Intervention** TBNA, EBUS-FNA, and EUS-FNA performed sequentially as a single combined procedure.

**Main Outcome Measure** Sensitivity for detecting mediastinal lymph node metastases, using pathologic confirmation and 6- to 12-month clinical follow-up as the criterion standard.

**Results** Among 138 patients who met all study criteria, 42 (30%) had malignant lymph nodes. EBUS-FNA was more sensitive than TBNA, detecting 29 (69%) vs 15 (36%) malignant lymph nodes ( $P=.003$ ). The combination of EUS-FNA and EBUS-FNA (EUS plus EBUS) had higher estimated sensitivity (93% [39/42]; 95% confidence interval, 81%-99%) and negative predictive value (97% [96/99]; 95% confidence interval, 91%-99%) compared with either method alone. EUS plus EBUS also had higher sensitivity and higher negative predictive value for detecting lymph nodes in any mediastinal location and for patients without lymph node enlargement on chest computed tomography.

**Conclusions** These findings suggest that EBUS-FNA has higher sensitivity than TBNA and that EUS plus EBUS may allow near-complete minimally invasive mediastinal staging in patients with suspected lung cancer. These results require confirmation in other studies but suggest that EUS plus EBUS may be an alternative approach for mediastinal staging in patients with suspected lung cancer.

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tial alternatives. Such methods include blind transbronchial needle aspiration (TBNA), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and, most recently, endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA).<sup>5</sup> We hypothesized that EBUS-FNA would be more accurate than TBNA and that the combination of EUS-FNA and EBUS-

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FNA (EUS plus EBUS) would provide complementary and complete staging of the mediastinum in patients with suspected lung cancer.

## METHODS

The study was approved by the Mayo Clinic institutional review board, and all patients provided written informed consent. Patients were included if they had known or suspected lung cancer on the basis of a lung or mediastinal abnormality on CT and if they had no pathologically proven extrathoracic metastases. Consecutive patients who met the study criteria were included, with no selection on the basis of mediastinal lymph node size or location. The first patient was enrolled on November 18, 2004, and the last on October 30, 2006. Data were locked for analysis on April 30, 2007, which allowed 6 months of follow-up after the last patient was enrolled.

### Noninvasive Staging

Computed tomography and PET were performed separately in all patients before invasive staging, and images were interpreted by the study radiologist (B.L.M.). Lymph nodes were considered enlarged if the short-axis diameter was 1 cm or greater as measured by CT.<sup>6</sup> The positron emission tomography images were correlated with the CT images; PET activity was classified by the standard uptake value and considered positive if the value was 2 or greater.

### TBNA, EBUS-FNA, and EUS-FNA Staging

TBNA, EBUS-FNA, and EUS-FNA were performed as a single combined procedure with the patient under conscious sedation. Bronchoscopic TBNA was performed first, followed immediately by EBUS-FNA. Both procedures were performed in each patient by 1 of 2 experienced pulmonologists (J.M.P., M.M.J.) trained in EBUS-FNA. EUS-FNA was performed immediately after TBNA and EBUS-FNA by 1 of 3 experienced gastroenterologists (M.B.W., M.R., T.A.W.) trained in EUS-FNA.

All procedures were performed blinded to the results of the others. Bronchoscopic TBNA is blinded, so the results of the TBNA were unknown to the pulmonologist at the time EBUS-FNA was performed. The gastroenterologist was not present in the procedure room during all TBNA and EBUS-FNA procedures, and the pulmonologist was not present during the EUS-FNA procedures.

After application of topical oropharyngeal anesthetic and administration of appropriate sedation with midazolam and fentanyl, a standard bronchoscope was passed transorally into the trachea and the bronchi were inspected. TBNA, with at least 3 fine-needle aspiration (FNA) passes, was performed at regions with enlarged lymph nodes on chest CT. EBUS-FNA was performed as previously reported by Vilmann et al.<sup>7</sup> Visible lymph nodes, regardless of size, were sampled using FNA. If more than 1 lymph node was present in a specific location, the largest lymph node was sampled. EUS-FNA was performed as previously described,<sup>8</sup> and lymph nodes were sampled by FNA in the same manner as for EBUS.

Thin-smear samples from FNA were prepared on site by a cytology technician using both air-dried slides for modified Romanovsky staining (Diff-Quik; Dade Behring Inc, Deerfield, Illinois) and alcohol-fixed slides for Papanicolaou staining. Rapid on-site evaluation was not used in any procedure. All slides were reviewed remotely by a staff pathologist, and the samples were classified as “nondiagnostic,” “benign,” “suspicious for malignancy,” or “malignant.” For analysis purposes, samples that were classified as suspicious or malignant were considered “positive,” and samples that were benign or nondiagnostic were considered “negative.”

### Surgery

Patients were evaluated for surgery on the basis of the American College of Chest Physicians guidelines.<sup>9</sup> In general, patients were considered for surgery if they had a solid lung mass that

was larger than 1 cm or that was increasing in size; if forced expiratory volume in 1 second and carbon monoxide diffusion capacity of the lung were greater than 80% of predicted values; and if they had no pathologically confirmed distant or N2 or N3 lymph node metastases. All surgeries were performed within 3 months of the staging tests. Patients who were not candidates for surgical resection and who had negative cytologic results were followed up with chest CT approximately every 6 to 12 months. Patients with malignant mediastinal lymph nodes by cytology were offered systemic chemotherapy and radiotherapy with or without subsequent surgery.

### Diagnostic Standard

The diagnostic standard for a positive result was pathologic confirmation of malignancy or a specific benign disease (eg, sarcoidosis) by any tissue-sampling method (FNA, open surgical biopsy, or mediastinoscopy/thoracoscopy). The diagnostic standard for a negative result was surgical sampling of the mediastinal lymph nodes by mediastinoscopy or thoracoscopy, open surgical exploration showing no disease, or 6 to 12 months of follow-up with no evidence of enlargement of lymph nodes in the mediastinum.

### Sample Size and Statistical Analysis

The sample size of 150 patients was chosen with the aim of providing at least 80% power at the 5% level of significance to detect at least a 20% difference in sensitivities between TBNA and EBUS-FNA. Demographic variables were summarized with medians and interquartile ranges for continuous variables and with frequencies and percentages for categorical variables. Binomial proportions and 95% exact confidence intervals (CIs) were used to estimate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each method of staging. Sensitivities were compared between methods using the

**Table 1.** Demographic Characteristics of Study Participants (N = 138)

Characteristic	Value
Age at bronchoscopy, median (IQR), y	69 (60-76)
Men, No. (%)	66 (48)
Location of primary tumor, No. (%)	
Lung	
Right upper lobe	32 (23)
Right middle lobe	4 (3)
Right lower lobe	15 (11)
Left upper lobe	12 (9)
Left lower lobe	7 (5)
Right hilar	1 (1)
Mediastinal only	65 (47)
Unknown	2 (1)
Procedure duration, median (IQR), min	
TBNA	15 (9-20)
EUS-FNA	21 (15-30)
EBUS-FNA	26 (20-32)
Procedure results, No. (%) <sup>a</sup>	
Positive	42 (30)
Negative	92 (67)
Unknown <sup>b</sup>	4 (3)

Abbreviations: EBUS-FNA, endobronchial ultrasound-guided fine-needle aspiration; EUS-FNA, transesophageal endoscopic ultrasound-guided fine-needle aspiration; IQR, interquartile range; TBNA, transbronchial needle aspiration.

<sup>a</sup>Positive and negative reflect final status according to the diagnostic standard, including pathologically confirmed lymph nodes and the 6-12 months of follow-up for negative as outlined in "Methods."

<sup>b</sup>Refused surgery.

**Table 2.** Final Histological Results

Histological Classification	Patients, No. (%) (N = 138)
Benign	51 (37)
Adenocarcinoma	38 (28)
Squamous cell carcinoma	16 (12)
Non-small cell lung cancer	13 (9)
Small cell lung cancer	7 (5)
Sarcoidosis	6 (4)
Lymphoma	4 (3)
Bronchioalveolar cell carcinoma	1 (1)
Carcinoid	1 (1)
Metastatic breast cancer	1 (1)

exact form of the McNemar test for paired proportions;  $P < .05$  was considered statistically significant. Confidence intervals for differences in proportions were constructed using the Tango score method for paired proportions.<sup>10</sup> When comparing the sensitivity of a combination approach with that of either of the component methods, a statistical test is not appropriate, because it is not possible for a combina-

tion to have lower sensitivity than that of its component parts. Analyses were performed using S-Plus version 8.0 (Insightful Corp, Seattle, Washington).

**RESULTS**

The combined TBNA/EBUS-FNA/EUS-FNA procedure was completed without complication in all 150 patients. The primary CT or PET images were not available for review for 12 patients; therefore, the remaining 138 patients were included in the study. TABLE 1 summarizes the demographic characteristics of the study participants. The final histological results for the participants are shown in TABLE 2.

The FIGURE shows the flow of screened and included patients through the study, along with major diagnostic tests and outcomes. Surgical procedures included thoracotomy with mediastinal exploration (n=33), lobectomy with mediastinal exploration (n=4), mediastinoscopy (n=4), and thoracoscopy (n=1). Malignant mediastinal lymph nodes were identified by surgery (thoracotomy with mediastinal exploration) in 3 patients: 1 had malignant subaortic and paraesophageal lymph nodes, and 2 had isolated malignant para-aortic lymph nodes. In 99 patients, no mediastinal lymph node malignancies were detected by FNA. These patients either refused surgery (n=4) or had no primary lung tumor and were followed up with surveillance CT.

**Comparison of Staging Methods**

TABLE 3 shows the estimated sensitivities and NPVs for all 3 staging methods and their paired combinations. Differences in sensitivities for selected pairs of methods are shown in TABLE 4. EBUS-FNA had higher sensitivity than TBNA (69% vs 36%,  $P = .003$ ), detecting 29 (vs 15) of the 42 malignant lymph nodes. EUS plus EBUS had higher sensitivity than any of the other methods (93% [39/42]; 95% CI, 81%-99%). Compared with either EUS-FNA or EBUS-FNA alone, the combination identified 10 more malignant lymph nodes, with sensitivity estimated to be 24% higher (95% CI, 12%-

39%) than either approach alone. According to the study definition of diagnostic positivity, all biopsy-based methods had specificities and PPVs of 100%. Estimated NPVs for the 6 staging methods are shown in Table 3. TBNA had the lowest estimated NPV (78% [96/123]; 95% CI, 70%-85%), and EUS plus EBUS had the highest (97% [96/99]; 95% CI, 91%-99%).

The mean number of lymph nodes sampled by EUS-FNA, EBUS-FNA, and TBNA was 1.41, 1.36, and 0.87, respectively; each method had a median of 1 lymph node sampled. The percentage of malignant lymph nodes detected by each procedure (number malignant/total number sampled) was 15% for TBNA, 19.7% for EBUS-FNA, and 22% for EUS-FNA.

**Location of Malignant Lymph Nodes**

TABLE 5 shows the location of malignant lymph nodes detected by each procedure and by subsequent surgery in the 68 patients with non-small cell lung cancer (including adenocarcinoma, squamous cell carcinoma, and bronchioalveolar cell carcinoma). EUS-FNA detected lymph nodes predominantly in the subcarina and posterior mediastinum (American Joint Committee on Cancer stations 7 and 5), and EBUS-FNA detected lymph nodes primarily in the subcarina and anterior mediastinum (stations 7, 2, 3, and 4). EUS-FNA access has now been expanded to include station-6 lymph nodes lateral to the aorta, which requires transaortic FNA. There was no obvious pattern to the 5 lymph nodes missed by the FNA procedures but detected by surgery in stations 5, 6, 7, and 9.

**CT and PET Results**

The estimated sensitivity of PET in this patient population was somewhat low (24% [10/42]; 95% CI, 12%-39%), although specificity was high (90% [86/96]; 95% CI, 82%-95%). For CT, the sensitivity was higher than that for PET (67% [28/42]; 95% CI, 50%-80%), although CT had poor specificity (53% [51/96]; 95% CI, 43%-63%). Thus, the

accuracy of both CT and PET were lower than that of EUS plus EBUS.

**Subgroup Analysis**

Four nonmutually exclusive subgroups were predefined to determine whether a single procedure would be adequate for diagnosis in certain patients, as defined by the location of the abnormal lymph nodes. For example, EUS-FNA is best suited to sample lymph nodes in the subcarinal, aortopulmonary window, paraesophageal, and pulmonary ligament regions.

Subgroup 1 (“EUS suited”) was defined as patients who presented with a PET-positive subcarinal node or in whom CT showed an enlarged lymph node in a subaortic, subcarinal, paraesophageal, or pulmonary ligament location. In this subgroup of 54 patients, EUS-FNA was not significantly more sensitive than EBUS-FNA (estimated sensitivities, 75% [15/20] vs 70% [14/20], respectively). The combination of EUS-FNA plus EBUS-FNA had a sensitivity of 100%. The NPVs of EUS-FNA, EBUS-FNA, and EUS plus EBUS were 87% (34/39), 85% (34/40), and 100% (34/34), respectively.

Subgroup 2 (“EBUS suited”) was defined as patients who presented with a PET-positive subcarinal node or with an enlarged lymph node in an upper paratracheal, lower paratracheal, or subcarinal location. In this subgroup of 74 patients, EBUS-FNA was more sensitive than EUS-FNA (estimated sensitivities, 76% [22/29] vs 69% [20/29], respectively). Both were less sensitive than the combination (100% [29/29]). The NPVs of EUS-FNA, EBUS-FNA, and EUS plus EBUS were 83% (45/54), 87% (45/52), and 100% (45/45), respectively, in this subgroup.

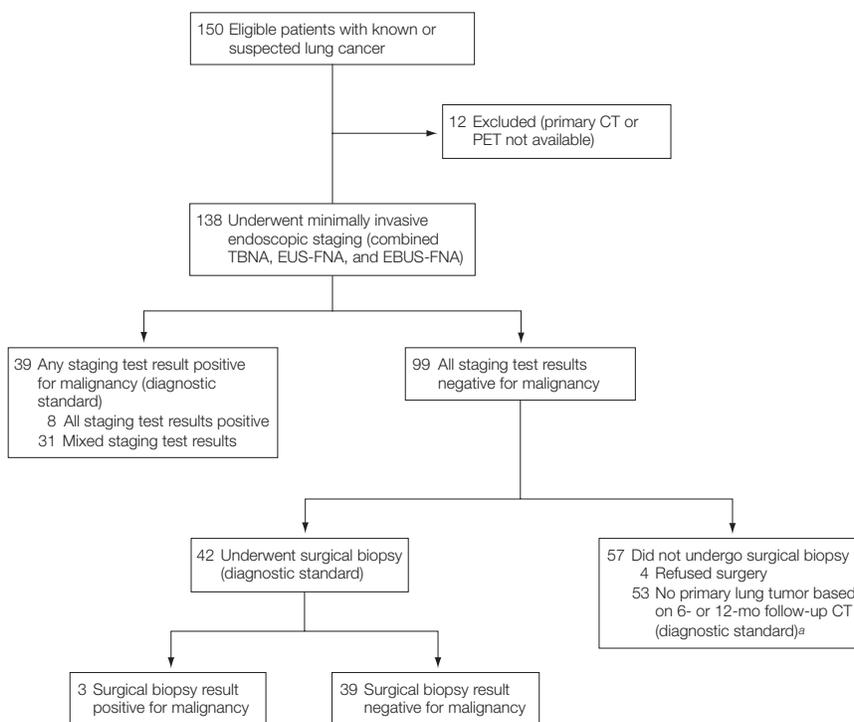
Subgroup 3 (“bronchoscopy suited”) was defined as patients who presented with a PET-positive subcarinal node or an enlarged lymph node in the subcarinal location. In this subgroup of 50 patients, the estimated sensitivity of TBNA (47% [9/19]) was lower than those of EUS-FNA (74% [14/19]), EBUS-FNA (68% [13/19]), and EUS plus EBUS (100%). The NPVs were 76% (31/41) for

TBNA, 86% (31/36) for EUS-FNA, 84% (31/37) for EBUS-FNA, and 100% (31/31) for EUS plus EBUS.

Subgroup 4 (“CT- and PET-negative mediastinum”) was defined as patients who had negative results by CT and PET; 60 study participants met this criterion. In this subgroup, TBNA had low esti-

mated sensitivity (17% [2/12]), whereas the estimated sensitivities of EUS-FNA, EBUS-FNA, and EUS plus EBUS were 67% (8/12), 50% (6/12), and 75% (9/12), respectively. The NPVs were 83% (48/58) for TBNA, 92% (48/52) for EUS-FNA, 89% (48/54) for EBUS-FNA, and 94% (48/51) for EUS plus EBUS.

**Figure.** Flow of Patients Through the Study and Detection of Malignant Mediastinal Lymph Nodes



CT indicates computed tomography; EBUS-FNA, endobronchial ultrasound-guided fine-needle aspiration; EUS-FNA, transesophageal endoscopic ultrasound-guided fine-needle aspiration; PET, positron emission tomography; TBNA, transbronchial needle aspiration.  
<sup>a</sup>The 57 patients with no mediastinal lymph node malignancies detected by fine-needle aspiration and who did not undergo surgical biopsy were included in the analysis.

**Table 3.** Estimated Sensitivities and Negative Predictive Values (NPVs) for Separate and Paired Procedures

Procedure	Fraction (%) [95% CI] <sup>a</sup>	
	Sensitivity	NPV
TBNA	15/42 (36) [22-52]	96/123 (78) [70-85]
EUS-FNA	29/42 (69) [53-82]	96/109 (88) [80-93]
EBUS-FNA	29/42 (69) [53-82]	96/109 (88) [80-93]
EUS-FNA + TBNA	33/42 (79) [63-90]	96/105 (91) [84-96]
EBUS-FNA + TBNA	32/42 (76) [61-88]	96/106 (91) [83-95]
EUS-FNA + EBUS-FNA	39/42 (93) [81-99]	96/99 (97) [91-99]

Abbreviations: CI, confidence interval; EBUS-FNA, endobronchial ultrasound-guided fine-needle aspiration; EUS-FNA, transesophageal endoscopic ultrasound-guided fine-needle aspiration; TBNA, transbronchial needle aspiration.  
<sup>a</sup>For sensitivity, fraction indicates No. of positive cases detected by test/No. positive by diagnostic standard. For NPV, fraction indicates No. of true-negative results/No. of true-negative plus false-negative results by the procedure.

**Sensitivity Analysis**

Four patients who had negative results by biopsy did not undergo surgery and did not have the required 12 months of follow-up to be considered as having true-negative results. For the primary analysis, however, they were assumed to be free of disease. For sensitivity analysis, we repeated the analyses assuming a worst-case scenario—that all 4 patients were positive for disease. The estimated sensitivities and NPVs for all methods were decreased, with EUS plus EBUS having an estimated sensitivity of 85% (39/46) and an NPV of 93% (92/99). Despite the lower sensitivities in this analysis, the sensitivity of EUS plus EBUS was still higher than that of all other approaches.

**COMMENT**

Our results show that EBUS-FNA is more accurate than standard TBNA for the detection of malignant mediasti-

nal lymph nodes. EUS plus EBUS is more accurate than any of these procedures alone. In this study, this combination provided nearly complete staging (NPV, 97%; PPV, 100%) of the mediastinum and was performed without procedural complications.

Accurate staging of lung cancer is critical for choosing the optimal therapy. Mediastinal lymph nodes are the most common site of metastases. Patients without evidence of mediastinal lymph node metastases are generally offered surgical resection, whereas those with metastases are treated with chemoradiotherapy with or without surgery. Noninvasive methods such as CT and PET are safe but have limited sensitivity and specificity, with PPVs of only 56% to 79% and NPVs of 83% to 93% for detection of mediastinal lymph node metastases.<sup>3</sup> The American College of Chest Physicians' guidelines for lung

cancer staging suggest that patients with abnormal lymph nodes on CT or PET, or centrally located tumors without mediastinal adenopathy, should undergo invasive staging.<sup>11</sup> The most common invasive methods are mediastinoscopy, TBNA, EUS-FNA, and EBUS-FNA.

Mediastinoscopy is a surgical procedure performed under general anesthesia and is considered the diagnostic standard (NPV, 89%; PPV, 100%), but it has limitations.<sup>11</sup> Mediastinoscopy is best suited for sampling lymph nodes in the pretracheal and paratracheal regions but has limited access to the inferior and posterior mediastinum and aortopulmonary window. Although generally safe, mediastinoscopy has a 2% risk of major morbidity and a 0.08% risk of mortality and is substantially more costly than EUS-FNA.<sup>11-13</sup> Proponents of mediastinoscopy cite its high NPV, particularly for patients without enlarged mediastinal lymph nodes.<sup>11</sup> In our study, the NPV of EUS plus EBUS was estimated to be 97%, approaching that of thoracotomy with mediastinal lymph node dissection.

Few trials have directly compared mediastinoscopy with an endoscopic staging method. In a trial by Larsen et al,<sup>14</sup> which compared EUS-FNA with mediastinoscopy in patients with paratracheal or subcarinal lymphadenopathy, EUS-FNA was significantly more accurate than mediastinoscopy overall and specifically in the subcarinal area. That study did not evaluate patients with enlarged pretracheal lymph nodes, a region in which mediastinoscopy is expected to be superior.<sup>14</sup>

Our findings suggest that EUS plus EBUS may be a substitute for mediastinoscopy in some cases. If mediastinoscopy had been performed only when results from EUS plus EBUS were negative, this surgical procedure would have been avoided in 28% (39/138) of patients in this study. If EUS plus EBUS had been used to completely replace mediastinoscopy (100% of patients), 97% would have been correctly labeled as negative.

**Table 4.** Selected Comparisons of Sensitivities

Comparison	Sensitivity Difference, Fraction (%) [95% CI] <sup>a</sup>	P Value <sup>b</sup>
EBUS vs TBNA	14/42 (33) [14-51]	.003
EUS + EBUS vs EUS + TBNA	6/42 (14) [5-28]	.03
EUS + EBUS vs EUS	10/42 (24) [12-39]	NA
EUS + EBUS vs EBUS	10/42 (24) [12-39]	NA
EUS + TBNA vs EUS	4/42 (10) [3-23]	NA
EUS + TBNA vs TBNA	18/42 (43) [30-59]	NA

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound-guided fine-needle aspiration; EUS, transesophageal endoscopic ultrasound-guided fine-needle aspiration; NA, not applicable because 1 test is a subset of another; TBNA, transbronchial needle aspiration.

<sup>a</sup>Fraction indicates No. of additional cases detected by 1 test (the first of each pair) compared with the other test/No. positive by diagnostic standard.

<sup>b</sup>By exact McNemar test.

**Table 5.** Locations of Malignant Lymph Nodes Detected by Each Procedure in Patients With Non-Small Cell Lung Cancer (n = 68)<sup>a</sup>

AJCC Station	No. of Lymph Nodes Detected, by Procedure <sup>b</sup>			
	TBNA	EUS	EBUS	Surgery
1	1	0	1	0
2	2	1	3	0
3	2	0	10	0
4	1	0	3	0
5	0	9	2	1
6	0	4	1	2
7	6	13	11	1
8	0	0	0	0
9	0	0	0	1

Abbreviations: AJCC, American Joint Committee on Cancer; EBUS, endobronchial ultrasound-guided fine-needle aspiration; EUS, transesophageal endoscopic ultrasound-guided fine-needle aspiration; TBNA, transbronchial needle aspiration.

<sup>a</sup>Also includes patients with adenocarcinoma, squamous cell carcinoma, and bronchioalveolar cell carcinoma.

<sup>b</sup>Some patients had multiple malignant lymph nodes.

Bronchoscopy is necessary in every patient with suspected lung cancer, at least to exclude occult contralateral cancer. For mediastinal lymph node metastases, TBNA has an NPV of approximately 75%, although estimates vary from 34% to 100%.<sup>11</sup>

EUS-FNA has emerged over the past 10 years as a valuable tool for mediastinal lymph node staging in lung cancer. EUS-FNA has a PPV greater than 99% and an NPV of 81%.<sup>11</sup> The primary reason for false-negative samples appears to be lymph node metastases located in sites inaccessible to EUS-FNA.<sup>15</sup> Because EUS-FNA is performed via the esophagus and ultrasonographic imaging does not penetrate air-filled structures, the region immediately anterior to the trachea is a "blind spot" for EUS-FNA. For this reason, EUS-FNA is best suited for sampling lymph nodes in the posterior mediastinum.

EBUS-FNA complements the mediastinal access of EUS-FNA. Because it does not share the blind spot of EUS-FNA, anterior mediastinal lymph nodes can be visualized.<sup>16</sup> Initial studies suggested that EBUS-FNA is highly accurate for mediastinal lymph node staging.<sup>16-28</sup> Herth et al<sup>28</sup> performed a randomized controlled trial of 200 patients who had disease staging by TBNA or EBUS-FNA. In patients with enlarged subcarinal lymph nodes, no significant difference was found between the yield of TBNA (74%) and EBUS-FNA (86%), but the study may have been underpowered to detect clinically important differences. In patients with enlarged lymph nodes in other mediastinal locations, EBUS-FNA had significantly higher yield than TBNA (84% vs 54%). Our study design differs in that all patients received TBNA, EBUS-FNA, and EUS-FNA, thus allowing paired comparison with substantially greater power to detect differences. Our study also focused on detection of malignant lymph nodes alone, whereas the study by Herth et al focused either on yield of malignant cells or on "adequate" cytology, defined as a "lymphocyte-positive specimen."<sup>28</sup>

Provision of high-quality EUS-FNA and EBUS-FNA testing is limited because of the need for training, specialized equipment, and combined endoscopic and bronchoscopic expertise. We sought to determine whether certain subgroups of patients, categorized on the basis of location of the adenopathy, could have adequate staging with only a single procedure. In all anatomical subgroups, EUS plus EBUS performed better than any procedure alone. Thus, training and organizational infrastructure to provide high-quality EUS plus EBUS services is critical.

Patients with suspicious lung tumors in the absence of mediastinal adenopathy on CT and PET, particularly those with centrally located tumors or intraparenchymal lymphadenopathy, have traditionally undergone mediastinal staging using mediastinoscopy followed by surgical exploration. EUS-FNA and EBUS-FNA separately have been shown to have good sensitivity in this patient population.<sup>15,21,29</sup> Our study confirms these findings and also shows that EUS plus EBUS has high sensitivity and NPV in this patient population.

This study has several limitations. First, we did not use rapid on-site evaluation of the cytologic samples to determine adequacy. Previous studies have suggested that on-site evaluation of TBNA specimens increases the cytologic yield but increases the cost and complexity of the procedure.<sup>30</sup> In contrast, rapid on-site evaluation of cytologic specimens does not increase the lymph-node yield of EUS-FNA.<sup>31</sup> To make equitable comparisons, we designed the study to exclude rapid on-site evaluation of cytologic specimens for all 3 procedures. Use of rapid on-site evaluation may have increased the overall sensitivity.

Second, it is possible that the high level of experience with EBUS-FNA in our study, and the subsequent high sensitivity, would be difficult to duplicate by other, less experienced, groups. However, we believe this unlikely, because EBUS-FNA is essentially a "new" procedure. The bronchoscopists in our study were experienced in standard

bronchoscopy but had only recently been trained in EBUS-FNA, and they still achieved a high level of sensitivity.

Third, TBNA had low sensitivity in our patient population. Most studies of individual procedures select patients who are most likely to have lymph nodes accessible to those procedures, thus resulting in higher sensitivity. For example, we previously reported higher sensitivity of EUS-FNA (sensitivity, 87%; specificity, 100%) in patients selected on the basis of the lymph nodes being in locations favorable for EUS-FNA.<sup>8</sup> Our current study enrolled consecutive patients with suspected lung cancer, with or without enlarged mediastinal lymph nodes, with no selection for the location of lymphadenopathy. This method likely allows for more broad generalization of the study results. It is unlikely that this limitation would affect the conclusion, however, because all 3 procedures had lower sensitivity when compared with other studies in more highly selected populations. Furthermore, the sensitivity of individual procedures was higher when we analyzed subgroups best suited for each procedure. Even in these subgroups, EUS plus EBUS had higher sensitivity and higher NPV than standard bronchoscopic TBNA. Subgroup comparisons should be interpreted with some caution, however, because of the small size of each specific group.

Fourth, it is possible that we have overestimated the absolute sensitivity of each procedure, because patients were followed up for a minimum of only 1 year if they had negative FNA results but were not candidates for surgery. It is possible that, in a few of these cases, mediastinal lymph nodes will eventually become malignant. However, we suspect that the effect of time on our estimate of sensitivity is small. Studies of follow-up after surgical resection show that most recurrences happen within 12 months, although they can occur up to 5 years later.<sup>32</sup> Furthermore, such studies most likely are biased toward later recurrences, because all visible (ie, bulkier) disease was

resected and only microscopic disease would be available for recurrence. Even if we have underestimated the absolute sensitivity, all procedures would most likely be affected equally. Thus, the significant difference we observed between procedures is unlikely to change.

## CONCLUSION

Our study suggests that EBUS-FNA and EUS-FNA are more sensitive than standard TBNA and that EUS-FNA in combination with EBUS-FNA achieves near-complete minimally invasive mediastinal staging in patients with suspected lung cancer. If these data are confirmed by other studies, they thus suggest that EUS plus EBUS may be an alternative method for surgical staging of the mediastinum in patients with suspected lung cancer.

**Author Contributions:** Dr Wallace had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Wallace, Pascual, Crook, Johnson, Odell.

**Acquisition of data:** Wallace, Pascual, Raimondo, Johnson, Al-Haddad, Gross, Pungpapong, Hardee, Odell.

**Analysis and interpretation of data:** Wallace, Pascual, Woodward, McComb, Crook.

**Drafting of the manuscript:** Wallace, Pascual, Woodward, Al-Haddad.

**Critical revision of the manuscript for important intellectual content:** Wallace, Pascual, Raimondo, Woodward, McComb, Crook, Johnson, Gross, Pungpapong, Hardee, Odell.

**Statistical analysis:** Wallace, Crook.

**Obtained funding:** Wallace.

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**Study supervision:** Wallace, Pascual.

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