

Mediastinoscopy in Patients With Lung Cancer and Negative Endobronchial Ultrasound Guided Needle Aspiration

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Background. Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) has been proposed as a safe, less-invasive alternative to mediastinoscopy to stage mediastinal lymph nodes in patients with lung cancer. We evaluated the negative predictive value of EBUS-TBNA in lung cancer patients suspected of having N2 nodal metastases.

Methods. This study is a single-institution retrospective review of cases with suspected or confirmed lung cancer undergoing mediastinoscopy after a negative EBUS-TBNA between June 2006 and February 2008.

Results. A total of 494 patients underwent EBUS-TBNA during the study period. Twenty-nine patients with suspected or confirmed lung cancer had a negative EBUS-TBNA and underwent subsequent mediastinoscopy. Mediastinoscopy was performed for findings suspicious of N2 disease based on noninvasive imaging. Mediastinoscopy found metastatic nodes in eight of 29 patients (28%)

for a patient-specific negative predictive value of EBUS-TBNA of 72% (95% CI, 56% to 89%). Mediastinal lymph node dissection found four further patients with positive N2 nodes (19%). The EBUS-TBNA and mediastinoscopy sampled the same lymph node station on 36 occasions in the 29 patients. The average lymph node size was 10 mm. Mediastinoscopy was positive in 5 of 36 stations, for a nodal-specific negative predictive value of EBUS-TBNA of 86% (95% CI, 75% to 97%).

Conclusions. Endobronchial ultrasound with transbronchial needle aspiration can effectively sample mediastinal lymph node stations in patients with lung cancer. However, in this early experience, 28% of patients with high clinical suspicion of nodal disease had N2 mediastinal nodal metastases confirmed by mediastinoscopy despite negative EBUS-TBNA.

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Current treatment algorithms for N2 level nodal metastases and stage IIIA non-small cell lung cancer involve either neoadjuvant or definitive chemoradiation therapy. Surgery is not typically performed as initial treatment. As a consequence, thorough preoperative staging of mediastinal lymph nodes has become a performance measure of quality care in lung cancer management [1]. Since surgical resection remains the single best curative option for true early stage lung cancer, pathologic tissue confirmation is desirable to prove that a suspicious nodal lesion is indeed malignant and therefore not exclude patients with potentially resectable cancers from surgical treatment on the basis of positive imaging studies alone.

Endobronchial ultrasound (EBUS) with transbronchial needle aspiration (EBUS-TBNA) has emerged as a less-

invasive, nonsurgical approach to obtain tissue from lymph nodes in the mediastinum. Recent reports have shown a high diagnostic yield, and some have even suggested superiority in direct comparison with mediastinoscopy [2]. It is still unclear how this technology should be incorporated into current algorithms for mediastinal staging. The primary objective of this study was to identify the false negative rate and negative predictive value (NPV) of EBUS-TBNA compared with mediastinoscopy in patients with known or suspected lung cancer and a negative EBUS-TBNA.

Patients and Methods

The study was approved by the Institutional Review Board of the Mayo Clinic College of Medicine. Between June 2006 and February 2008, 494 patients at the Mayo Clinic, Rochester, Minnesota, underwent EBUS-TBNA for evaluation of mediastinal lymph nodes. Within this group, 29 patients had suspected or confirmed lung cancer, a negative EBUS-TBNA, and a high clinical suspicion of mediastinal metastases based on lymph node size by computed tomography (CT) scan and (or) meta-

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Abbreviations and Acronyms

CT	= computed tomography
EBUS	= endobronchial ultrasound
EBUS-TBNA	= endobronchial ultrasound with transbronchial needle aspiration
EUS-FNA	= endoscopic ultrasound with fine needle aspiration
MLND	= mediastinal lymph node dissection
NPV	= negative predictive value
NSCLC	= non-small cell lung cancer
PET	= positron emission tomography
TBNA	= transbronchial needle aspiration

bolic activity on positron emission tomography (PET) scan. A high clinical suspicion of mediastinal metastasis was defined as either a lymph node of more than 1 cm in its minor axis in CT or a positive mediastinal lymph node station PET-CT. Mediastinoscopy was performed for each of these patients and constitute the cohort identified for retrospective analysis. Patients with positive lymph nodes for tumor cells on EBUS-TBNA were referred for neoadjuvant or definitive chemoradiation therapy according to disease stage. Those with negative biopsies were referred for surgical resection and mediastinal lymph node dissection (MLND) when the suspicion of mediastinal disease was low based on CT and PET scan.

The medical records of the 29 patients undergoing mediastinoscopy with a negative EBUS-TBNA were reviewed. Size and location of the sampled lymph nodes by CT scan, 18F-fluorodeoxyglucose uptake on PET, findings on the bronchoscopy, final pathology, and cytology reports were documented. In the first instance, we calculated the NPV of EBUS-TBNA compared with mediastinoscopy, regardless of the lymph node location that was sampled (patient-specific analysis). The EBUS-TBNA was considered negative for malignancy when no malignant cells were obtained from any of the sampled locations, regardless of which or how many mediastinal stations were sampled. Mediastinoscopy results were analyzed in the same manner. Lymph node stations sampled by EBUS-TBNA were matched with the stations sampled by mediastinoscopy to calculate the NPV of EBUS-TBNA compared with mediastinoscopy for individual nodal stations (nodal-specific analysis). We also compared the results of negative mediastinoscopies with the results of MLND in a patient and nodal-specific manner as described above.

Radiology

Both CT scan and PET-CT scan were performed in the majority of patients. The CT scans were reviewed for the presence of adenopathy (lymph nodes more than 1 cm in their shortest axis) and its location. Lymph nodes were classified according to the mediastinal lymph node map described by Mountain and Dresler [3]. Metabolically

active lymph nodes (more than 1.5-fold increase over background) of any size were identified on PET-CT.

Endobronchial Ultrasound With Transbronchial Needle Aspiration

Bronchoscopy was performed with moderate sedation. The results of the cytologic examination were classified as negative or positive based on the presence of malignancy. Three needle passes were obtained at each lymph node station sampled. Rapid on-site evaluation for cytology was not routinely used.

Mediastinoscopy

Mediastinoscopy was done on a selective basis depending on the findings of noninvasive staging but all 29 patients in the cohort had a mediastinoscopy. Biopsies from station 4R, 7, and 4L were routinely obtained. Biopsies were also obtained from other locations when lymph nodes were identified.

Mediastinal Lymph Node Dissection

The MLND was performed as part of lung resection surgery. When the surgical intervention was done on the right side mediastinal lymph node stations 2R, 4R, 7, 8, and 9 were removed, as well as any other significant lymph nodes found during surgery. For left-sided tumors, lymph nodes from mediastinal stations 5, 6, 7, 8, and 9 were removed. In all patients the intrapleural lymph nodes were removed with the pulmonary specimen.

Gold Standard

The gold standard positive was the finding of malignancy during mediastinoscopy or MLND. For a gold standard negative, patients had to have normal lymph node tissue in the mediastinal nodes sampled during MLND.

Statistics

The NPV was calculated using the following formula: number of true negatives / (number of true negatives + number of false negatives). The resulting NPV was expressed with its 95% confidence interval.

Results

Twenty-nine patients with negative EBUS-TBNA and a high suspicion of mediastinal disease based on CT or PET-CT underwent mediastinoscopy (Fig 1). All patients had a CT scan performed and 26 of 29 patients (90%) also had a PET-CT scan. Mediastinoscopy found lymph node metastases in eight patients (28%). The patient-specific NPV of EBUS-TBNA compared with mediastinoscopy was 72% (95% CI, 56% to 89%). These eight patients with N2 mediastinal disease discovered during mediastinoscopy were referred for neoadjuvant treatment, while the remaining patients underwent pulmonary resection of their malignancy with MLND. In these 21 patients with negative EBUS and mediastinoscopy, 4 patients were found to have positive mediastinal lymph nodes when MLND was performed at the time of pulmonary resec-

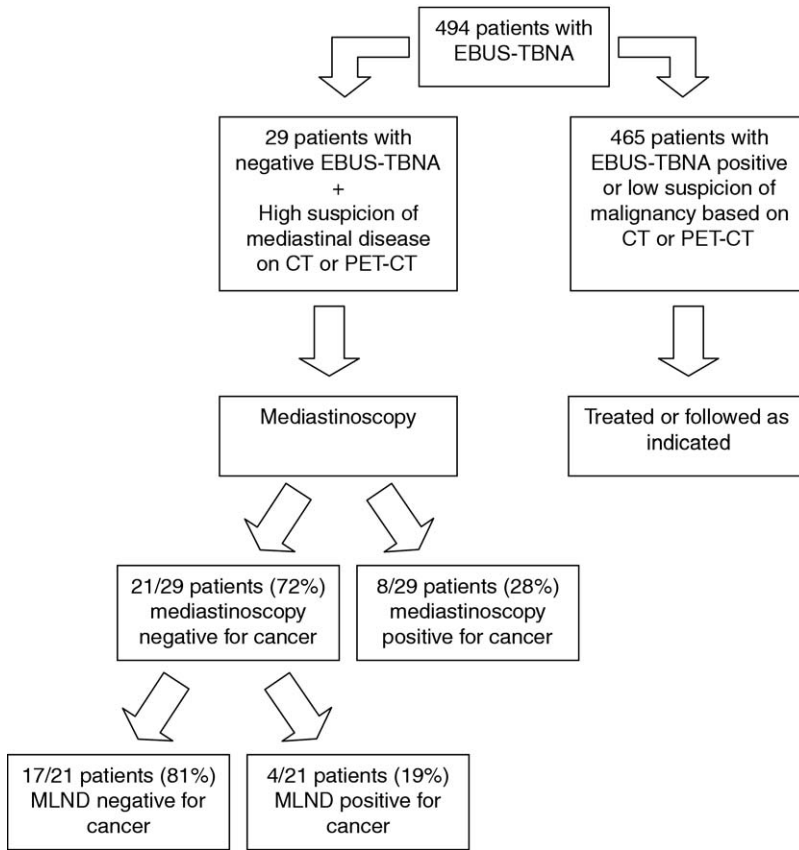


Fig 1. Flowchart of the 494 patients who underwent endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) in the series. (CT = computed tomography; MLND = mediastinal lymph node dissection; PET = positron emission tomography.)

tion. The patient-specific NPV of mediastinoscopy after a negative EBUS was 81% (64% to 98%).

On average, mediastinoscopy sampled more lymph nodes stations per patient than EBUS-TBNA (2.10 ± 0.61 vs 1.58 ± 0.61). Both tests sampled the same lymph node station in 36 occasions (Table 1). The median size of the lymph nodes that were sampled was 10 mm in the minor axis (range, 5 to 30 mm). The PET-CT scan evaluation was available in 34 of 36 lymph node stations (94%): in 19 (56%) occasions it showed metabolically active lymph nodes, whereas in 15 (44%) it did not. The EBUS-TBNA sampled station 4R 18 of 36 times (50%), station seven 14 of 36 times (39%), and station 4L 4 of 36 times (11%). In five of these 36 lymph node stations, which were EBUS negative, mediastinoscopy was positive for cancer, for a nodal-specific NPV of EBUS-TBNA of 86% (95% CI, 75%

to 97%). The median lymph node size of the five stations that were negative with EBUS-TBNA and found to be positive at mediastinoscopy was 18 mm (range, 5 to 30 mm). The PET-CT scan was done in four of these five cases and was positive in three. The EBUS-TBNA showed negative results in all five of these lymph node stations (lymphocytes were seen consistent with the sampled station), three times in station 4R (60%) and two in station 7 (40%). The NPV at station 4R was 83% (95% CI, 66% to 100%), while at station 7 it was 86% (95% CI, 67% to 100%).

Fifteen lymph node stations were PET negative and EBUS-TBNA negative. In one of these stations (station number 4R) mediastinoscopy found lymph node metastases. The combined NPV of PET and EBUS-TBNA compared with mediastinoscopy was 93% (95% CI, 81% to 100%).

Twenty-one EBUS-TBNA negative and mediastinoscopy negative lymph node stations were dissected during thoracotomy. Lymph node metastases were found in four of these mediastinal lymph node stations at MLND. The nodal-specific NPV of mediastinoscopy with negative EBUS compared with MLND was 81% (95% CI, 64% to 98%). In all four of these patients EBUS-TBNA and mediastinoscopy showed lymphoid tissue with no tumor cells, two times in station 4R and two times in station 7. The mean size of these four lymph nodes was 14.5 mm (range 13.6 to 18 mm). Three were metabolically active on PET scan while one was not.

Table 1. Negative Lymph Node Stations Sampled by EBUS-TBNA and Subsequent Mediastinoscopy Results

Lymph Node Station Sampled	No. Of Times Sampled (%)	Mediastinoscopy Positive Findings (%)	Mediastinoscopy Negative Findings (%)
4R	18 (50)	3 (17)	15 (83)
7	14 (39)	2 (14)	12 (86)
4L	4 (11)	0 (0)	4 (100)

EBUS-TBNA = endobronchial ultrasound with transbronchial needle aspiration.

Comment

The CT scan has a sensitivity of 50% to 76% and specificity between 55% and 86% for predicting metastatic involvement of mediastinal lymph nodes when they are greater than 1 cm in the short axis [4-6]. Positron emission tomography has emerged as a useful tool to evaluate the mediastinum with a sensitivity and specificity of 83% to 91% and 70% to 91%, respectively [6, 7]. However, tissue diagnosis is still desirable to prove malignancy and to avoid excluding potential surgical candidates from curative resection. Several methods can be used to achieve a histologic diagnosis of abnormal lymph nodes in the mediastinum. TBNA during bronchoscopy can provide an opportunity for sampling mediastinal lymph nodes. However, TBNA is limited to sampling nodes that are adjacent to accessible airways. It is less useful for small lymph nodes and its diagnostic yield varies widely between 20% and 70%, with a sensitivity and specificity of 76% and 96%, respectively, based on the size and location of the lymph nodes, stage of the disease, and operator experience [8-10]. Mediastinoscopy offers the ability to sample tissue from all paratracheal lymph nodes and the subcarinal space under direct vision. It is the most specific test but is an invasive procedure, requiring general anesthesia, that carries a small but measurable risk of potentially significant complications, with morbidity between 0.6% to 3%, risk of hemorrhage between 0.1% and 0.6%, and mortality of 0% to 0.3% [11-14].

Data continue to emerge for the results of EBUS-TBNA in the diagnosis of metastatic mediastinal lymph nodes in patients with non-small cell lung cancer and is still unclear how it compares with mediastinoscopy, which remains the gold standard in the preoperative staging of the mediastinum [2, 6, 15, 16]. We report in this study a comparison of EBUS-TBNA with mediastinoscopy in patients for which EBUS-TBNA was negative for malignancy and the clinical suspicion for mediastinal metastases was high based on noninvasive imaging. This reflects the initial EBUS-TBNA experience at our institution and the purpose was to perform a direct comparison with mediastinoscopy.

Studies similar to this include the prospective study of Ernst and colleagues [2] who reported a sensitivity of 87%, specificity of 100%, and negative predictive value of 78% of EBUS-TBNA compared to surgical lymph node dissection. Similar values were also calculated for mediastinoscopy and compared with EBUS-TBNA. They reported a sensitivity for mediastinoscopy of 68% and a negative predictive value of 59%. They concluded that EBUS-TBNA performed better than mediastinoscopy, suggesting that EBUS-TBNA has better access to some stations in the mediastinum such as the more posterior portions of the subcarinal space. However, it is interesting to note that the negative predictive value reported for mediastinoscopy was well below that reported in the literature [12, 17] as well as the NPV of 81% that we found in the current study.

We did not calculate sensitivity and specificity for EBUS-TBNA, as these statistics depend on the number of

true positive results and we do not refer patients with EBUS-TBNA results positive for malignancy for confirmatory mediastinoscopy. The possibility of having false positive results for EBUS-TBNA does exist, but avoiding passing the needle through malignant mucosa and being cautious about cross contamination between needles should mitigate this possibility.

The average sensitivity reported for mediastinoscopy is around 80%, with an NPV of almost 90% [17]. Many of the false negative results typically come from lymph node stations that are not accessible by this technique. We found in our study that mediastinoscopy had a NPV of 81% for both patient-specific and nodal-specific analyses, respectively. Our results did not correlate with the NPV found for mediastinoscopy of 59% reported by Ernst and colleagues [2]. However, when we compared EBUS-TBNA with mediastinoscopy, the negative predictive value of 78% was similar to ours.

We divided the analysis in two parts. First, we calculated how many times mediastinoscopy found metastatic lymph nodes that were missed by EBUS-TBNA, regardless of whether or not the same lymph node station was sampled. In this situation the NPV was 72%. Then, we compared lymph node stations where both techniques sampled the same location and found a NPV of 86%. These results are quite different from the report by Yasufuku and colleagues [6] of EBUS-TBNA having a NPV of 97.5% when compared with MLND. They did their analysis based on 200 punctures, finding only two patients with indeterminate results on EBUS-TBNA and malignancy upon MLND. They concluded that EBUS-TBNA has higher sensitivity, specificity, positive predictive value, and negative predictive value than CT and PET scan, but they did not compare EBUS-TBNA with mediastinoscopy.

It should be recognized that many of these reports, including ours, represent retrospective analyses and are not prospective, randomized clinical trials. Patients with lung cancer and mediastinal disease represent a heterogeneous group of patients, ranging from patients with occult N2 or single station disease to patients with bulky mediastinal adenopathy. We believe that the false negative rate of any preoperative staging procedure would be different in these situations. The answers for all these issues will only be addressed satisfactorily by a randomized controlled trial comparing EBUS-TBNA and mediastinoscopy with MLND as the gold standard applied in all cases of negative disease. Further examples of prospective trials performed to date include the study by Wallace and colleagues [15] comparing endoscopic ultrasound with fine needle aspiration, TBNA, and EBUS-TBNA. They developed a minimally invasive algorithm for the diagnosis of mediastinal disease in 138 patients suspected of having lung cancer. They found a negative predictive value of 97% when using the three mentioned methods combined to diagnose mediastinal metastases. However, they did not address the potential role for mediastinoscopy in this pathway.

In our study, only patients with suspected or biopsy proven lung cancer, clinical suspicion of mediastinal

disease, and negative EBUS-TBNA were referred for mediastinoscopy. This is demonstrated by the noninvasive evaluation of these lymph nodes showing a mean size of 10 mm, with 56% PET positive. In this specific situation, we found that in 28% of patients EBUS-TBNA could be falsely negative and miss lymph node metastases that could be diagnosed by mediastinoscopy. We believe that EBUS-TBNA can sample mediastinal lymph nodes effectively given the correlated results with the findings on mediastinoscopy in the majority of the patients. However, in patients with lung cancer, negative EBUS-TBNA and noninvasive staging suspicious for mediastinal disease, mediastinoscopy should be considered given the potential false negative rate of EBUS-TBNA.

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INVITED COMMENTARY

With the introduction of positron-emission tomographic scanning and endobronchial ultrasound (EBUS) into common practice more than a decade ago, many (nonsurgeons) talked of how mediastinoscopy would soon become obsolete. However, with the growing number of reports of head-to-head comparisons of these different diagnostic modalities to mediastinoscopy, EBUS has emerged as the primary competitor. Although EBUS has fairly high accuracy, sensitivity, and specificity, it remains imperfect.

Defranchi and colleagues [1] report their experience of a select group of patients with a high suspicion or diagnosis for non-small cell lung cancer and the notion of mediastinal lymph node involvement by computed tomographic or positron-emission tomographic criteria [1]. In this series of 29 patients who had a negative EBUS biopsy of mediastinal lymph nodes, mediastinoscopy was subsequently performed. They report a patient- and nodal-specific negative predictive value of 72% and 86%, respectively. These numbers are a little lower than published reports, and perhaps could be explained by where along the learning curve these study patients lie. Unfortunately, the obvious limitations of this retrospective study in a small number of patients make the results difficult to conclude that EBUS should be the primary staging modality for the mediastinum in

similar patients with nonsmall cell lung cancer. Unfortunately, the following were not presented: whether N1 nodes were biopsied or if a rapid on-site evaluation by a cytopathologist was available to increase the yield.

There remains some variability in published EBUS statistics, which raises the question of how to interpret negative EBUS results when there remains a high clinical index of suspicion. In their 2007 clinical practice guidelines on invasive staging of the mediastinum [2], the American College of Chest Physicians reviewed the diagnostic results of 25 papers using mediastinoscopy and EBUS. The sensitivity of both procedures was 90%, but the false negative rates were 10% and 24%, respectively. However, their conclusions and suggestions were dependent on why the EBUS was originally performed. Pertinent to Defranchi and colleagues' [1] article, patients with discreet mediastinal lymph node enlargement, mediastinoscopy, or EBUS is reasonable, but the false negative rate is lower for the former. If EBUS yields a negative result, this should be confirmed by a mediastinoscopy.

Mediastinoscopy in the hands of an experienced thoracic surgeon still remains a minimally invasive approach in staging the upper mediastinum, with the very rare case of any complications, extremely low false negative re-