A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer

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Objective: The study objective was to compare endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) with mediastinoscopy for mediastinal lymph node staging of potentially resectable non–small cell lung cancer.

Methods: Patients with confirmed or suspected non–small cell lung cancer who required mediastinoscopy to determine suitability for lung cancer resection were entered into the trial. All patients underwent EBUS-TBNA followed by mediastinoscopy under general anesthesia. If both were negative for N2 or N3 disease, the patient underwent pulmonary resection and mediastinal lymphadenectomy.

Results: Between July 2006 and August 2010, 190 patients were registered in the study, 159 enrolled, and 153 were eligible for analysis. EBUS-TBNA and mediastinoscopy sampled an average of 3 and 4 lymph node stations per patient, respectively. The mean short axis of the lymph node biopsied by EBUS-TBNA was 6.9 ± 2.9 mm. The prevalence of N2/N3 disease was 35% (53/153). There was excellent agreement between EBUS-TBNA and mediastinoscopy for mediastinal staging in 136 patients (91%; Kappa, 0.8; 95% confidence interval, 0.7–0.9). Specificity and positive predictive value for both techniques were 100%. The sensitivity, negative predictive value, and diagnostic accuracy for mediastinal lymph node staging for EBUS-TBNA and mediastinoscopy were 81%, 91%, 93%, and 79%, 90%, 93%, respectively. No significant differences were found between EBUS-TBNA and mediastinoscopy in determining the true pathologic N stage (McNemar's test, $P = .78$). There were no complications from EBUS-TBNA. Minor complications from mediastinoscopy were observed in 4 patients (2.6%).

Conclusions: EBUS-TBNA and mediastinoscopy achieve similar results for the mediastinal staging of lung cancer. As performed in this study, EBUS-TBNA can replace mediastinoscopy in patients with potentially resectable non–small cell lung cancer. (J Thorac Cardiovasc Surg 2011;142:1393-400)

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Lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer death worldwide despite advances in imaging, surgery, and multimodality treatment.[1] Accurate staging of the disease is mandatory to determine the prognosis and appropriate treatment. The most significant treatment decision lies in the distinction between those patients who can benefit from surgical resection and those who should receive chemotherapy and radiation therapy or both. The existence of metastatic contralateral adenopathy (N3) currently contraindicates surgery. Patients with ipsilateral lymph node metastasis (N2) may be considered for neoadjuvant therapy followed by surgery on the basis of studies reporting improved survival with this treatment approach.[2] Therefore, preoperative evaluation of mediastinal lymph nodes is important for selecting the optimal treatment.

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Funding: The EBUS equipment for the study was loaned from Olympus Medical Systems. Disposables used for EBUS-TBNA were provided by Olympus Medical Systems.

Disclosures: K.Y. has received research support funding from Olympus Medical Systems.

Read at the 91st Annual Meeting of The American Association for Thoracic Surgery, Philadelphia, Pennsylvania, May 7-11, 2011.

Received for publication May 10, 2011; revisions received Aug 7, 2011; accepted for publication Aug 25, 2011; available ahead of print Oct 3, 2011.

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0022-5223/$36.00

doi:10.1016/j.jtcvs.2011.08.037

Abbreviations and Acronyms

CP-EBUS	= convex probe endobronchial ultrasound
CT	= computed tomography
EBUS-TBNA	= endobronchial ultrasound-guided transbronchial needle aspiration
EUS-FNA	= endoscopic ultrasound-guided fine-needle aspiration
NSCLC	= non–small cell lung cancer
PET	= positron emission tomography
ROSE	= rapid on-site evaluation
TBNA	= transbronchial needle aspiration

At present, the best means to assess lymph node involvement is by direct sampling. The current gold standard method to obtain such direct sampling is by mediastinoscopy.[3] Mediastinoscopy has the ability to access samples of the paratracheal lymph node stations (levels 2R, 2L, 4R, 4L), the anterior subcarinal lymph node station (level 7), and the hilar lymph node station (level 10). Mediastinoscopy is performed under general anesthesia. Complications related to mediastinoscopy are extremely low when performed by experienced surgeons.[4] Given the invasive and costly nature of mediastinoscopy, there has been considerable interest recently in the development of techniques that allow minimally invasive sampling of mediastinal lymph nodes.

Minimally invasive techniques use needle biopsy to obtain tissue samples from mediastinal lymph nodes.[5,6] Needle biopsy techniques include transbronchial needle aspiration (TBNA), transthoracic needle aspiration, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and, most recently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

EBUS-TBNA is a minimally invasive method of mediastinal biopsy performed under direct real-time endobronchial ultrasound guidance.[7-18] EBUS-TBNA allows access to the paratracheal lymph node stations (levels 2R, 2L, 4R, 4L), the subcarinal lymph node (level 7), and the hilar, interlobar, and lobar lymph nodes (levels 10, 11, and 12). Previous studies, including systematic reviews and meta-analyses, have demonstrated a major impact of EBUS-TBNA on management of patients with non–small cell lung cancer (NSCLC), with a diagnostic yield comparable to mediastinoscopy. However, there have been few comparative studies involving direct comparison of EBUS-TBNA and the gold standard mediastinoscopy.[11] The purpose of the current study was to compare EBUS-TBNA with mediastinoscopy for mediastinal lymph node staging of NSCLC.

MATERIALS AND METHODS

Study Design

This was a prospective, controlled trial performed in patients with confirmed or suspected NSCLC who required a mediastinoscopy as part of their staging investigations of the mediastinum to determine suitability for lung cancer resection. This study was approved by the University Health Network Institutional Research Ethics Board (University Health Network REB#06-0085-C). A written informed consent was obtained from all patients. All patients received chest and upper abdominal computed tomography (CT) with contrast injection. CT was used for assessment of resectability of the primary tumor, evaluation of mediastinal lymph nodes, and exclusion of distant metastases. Lymph nodes with the short axis larger than 1 cm on chest CT were classified as positive for malignancy by CT criteria. Positron emission tomography (PET) was available for patients who were eligible to undergo PET scan during our study period (n = 88). Between July 2006 and August 2010, 190 patients were registered and 153 were eligible for evaluation (Figure 1).

The inclusion and exclusion criteria for the study were as follows:

Inclusion criteria. (1) Patients aged 18 years or older and (2) patients with confirmed or suspected NSCLC who required a mediastinoscopy as part of their staging investigations of the mediastinum to determine suitability for lung cancer resection.

Exclusion criteria. (1) Patients who were deemed on clinical grounds to be medically unfit for a bronchoscopy or a mediastinoscopy, (2) patients who had verified stage IV disease or who were not appropriate for lung cancer resection by virtue of technical inoperability, (3) patients with known small cell lung cancer, (4) patients with a high clinical suspicion of lymphoma, and (5) patients unable to give informed consent.

After the administration of a general anesthetic, all patients underwent EBUS-TBNA as detailed below. All patients then underwent standard cervical mediastinoscopy in the same setting. Each patient served as his/her own control. The surgeon was blinded to the pathologic findings of EBUS-TBNA. The on-site cytopathologist reported the specimen as ''adequate'' or ''inadequate'' for diagnosis. Both EBUS-TBNA and mediastinoscopy were performed in all patients even if EBUS-TBNA result yielded N2 or N3 disease. If there was no evidence of N2 or N3 disease on EBUS-TBNA or mediastinoscopy samples, patients underwent thoracotomy, pulmonary resection, and mediastinal lymphadenectomy at the same setting or at a different time.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

The convex probe endobronchial ultrasound (CP-EBUS) was used to perform EBUS-TBNA (BF-UC160F-OL8, Olympus, Tokyo, Japan). The CP-EBUS is integrated with a convex transducer (7.5 MHz) that scans parallel to the insertion direction of the bronchoscope. The ultrasound image is processed in a dedicated ultrasound scanner (EU-C60, Olympus). Static ultrasound images were obtained, and the size of lesions were measured in 2 dimensions. Doppler mode imaging was used selectively.

After the induction of general anesthesia, patients were intubated with an endotracheal tube size 8 or greater or a laryngeal mask airway. Conventional flexible bronchoscopy was first performed, followed by examination of the mediastinum using the CP-EBUS. The location and size of the lymph nodes (ipsilateral and contralateral) were characterized and classified as N1, N2, or N3. A dedicated 22-gauge needle (NA-201SX-4022, Olympus) was used to perform all EBUS-TBNA procedures as previously described.[7,8] In brief, a dedicated needle equipped with a protective sheath was first passed through the working channel of the bronchoscope. After visualizing the lymph node, the needle was passed out of the sheath, through the airway, and into the lymph node. After penetration into the lymph node, the internal stylet was used to clean out the internal lumen clogged with bronchial membrane or cartilage. The internal stylet was then removed, and negative pressure was applied with a syringe. The

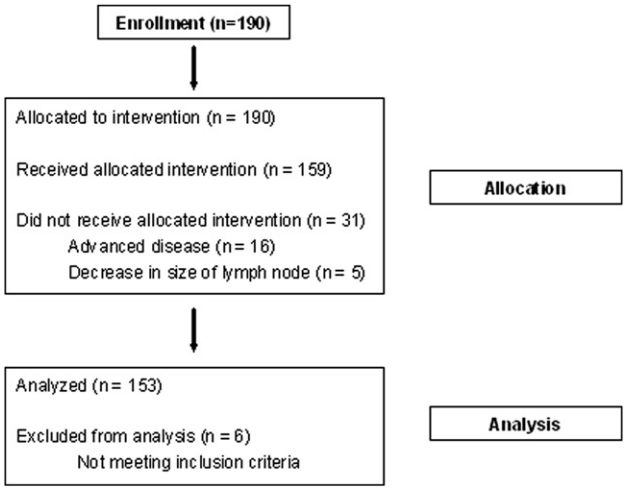

FIGURE 1. Flow chart showing enrollment, allocation, and analysis of 190 patients who were registered in the study, of whom 153 were eligible for analysis. Thirty-one patients did not enter the study after registration because of advanced disease (16), decrease in size of lymph node (5), and patient withdrawal (10). Six patients were excluded after the procedure because of advanced disease.

needle was moved back and forth inside the lymph node. Finally, the needle was retrieved and the internal stylet was used once again to push the specimen out onto a slide for cytologic examination, followed by a needle rinse in 15 mL of sterile saline. Smears were air dried and fixed in modified Carnoy's solution. The air-dried smears were stained with a modified Field's stain and evaluated by an on-site cytopathologist to confirm ''adequate'' cell material. Adequate cell material was defined as sufficient material for a specific diagnosis or the presence of lymphocytes on the specimen. If adequate tissue was not identified by rapid on-site evaluation (ROSE) after 5 passes, the biopsy of that site was terminated. A modified Papanicolaou stain was used for the Carnoy's fixed slides. The needle rinse was processed by cell block or ThinPrep slide production, and light microscopy was carried out by a cytopathologist (Figure E1).

EBUS-TBNA was performed by a thoracic surgeon (KY, AP, GD, MDP, TW, MJ, SK) responsible for the patient. Contralateral lymph nodes were sampled first followed by midline or ipsilateral lymph nodes. Where multiple nodes were seen, the most suspicious node in each group was targeted. Suspicious nodes are defined as round, well demarcated, and echo-poor. Different needles were used for each lymph node station to prevent cross-contamination. The localization of the lymph nodes was described according to the 7th TNM classification for lung cancer.[19] EBUS-TBNA was performed for all lymph nodes greater than 5 mm in CT short-axis diameter or suspicious lymph nodes on EBUS.

Mediastinoscopy

Standard cervical mediastinoscopy was performed immediately after EBUS-TBNA by a thoracic surgeon (KY, AP, GD, MDP, TW, MJ, SK) experienced in the technique. The same surgeon or different surgeons performed the EBUS-TBNA and mediastinoscopy, but the cytology results of EBUS-TBNA were blinded to the surgeon performing the mediastinoscopy. The paratracheal and subcarinal lymph node stations were systematically dissected, and lymph nodes from stations 2R, 4R, 2L, 4L, and 7 were evaluated. All stations were investigated, and if lymph nodes were identified, biopsies were performed irrespective of their size or appearance. The histologic samples underwent quick section or regular pathologic evaluation. Adequate sampling was defined as sufficient material for a specific diagnosis or presence of lymphoid tissue.

Pulmonary Resection

If there was no evidence of N2 or N3 disease on the EBUS-TBNA and mediastinoscopy samples, patients underwent surgical resection of the tumor at the same setting or a different time. Pulmonary resection and a systematic nodal dissection were performed in every patient by a thoracotomy or video-assisted thoracic surgery. The results of the surgical pathology were subsequently correlated with the results from the EBUS-TBNA and mediastinoscopy.

Statistical Analysis

Patient demographics and disease characteristics were summarized using descriptive statistics. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated. A true negative (N0/N1) was defined as patients with no N2 or N3 lymph node metastases evaluated by EBUS-TBNA and mediastinoscopy, and confirmed by surgical-pathologic examination. Otherwise, the final pathology N stage was taken as the highest grade among EBUS-TBNA, mediastinoscopy, and surgical N stage. The agreement between EBUS-TBNA and the gold standard mediastinoscopy was quantified using Cohen's Kappa statistics (K) and its 95% confidence interval (CI). The guideline for interpreting Kappa is greater than 0.75 as excellent, 0.40 to 0.75 as fair to good, and less than 0.40 as poor agreement.[20] The nonparametric McNemar's test was also performed to test whether there were significant differences between the 2 methods in yielding the correct/incorrect final pathology N stage for each patient in a paired comparison. All statistical analyses were performed using SAS (v9.2; SAS Institute Inc, Cary, NC).

RESULTS

Between July 2006 and August 2010, 190 patients were registered for the study and 159 cases were enrolled (Figure 1). Thirty-one patients did not proceed after registration because of advanced disease (16), decrease in lymph node size on follow-up imaging (5), or patient withdrawal (10). Six patients were excluded after the procedure because of advanced disease, leaving 153 available for analysis. The characteristics of these 153 evaluable patients and the details of primary lung cancer are shown in Table 1. The majority of the patients had cN0/1 disease based on imaging ($n = 97$, 64%). The mean short axis of the lymph nodes biopsied by EBUS-TBNA was 6.9 ± 2.9 mm. Mediastinoscopy and EBUS-TBNA were performed by 7 surgeons. The mean time for EBUS-TBNA was 20.2 ± 8.1 minutes.

The numbers of mediastinal lymph nodes sampled by EBUS-TBNA and mediastinoscopy from various lymph node stations are shown in Table 2. EBUS-TBNA sampled 426 lymph nodes (average 3/patient), and mediastinoscopy sampled 573 lymph nodes (average 4/patient).

There were 8 false-negative lymph node stations on EBUS-TBNA compared with 14 false-negative lymph node stations on mediastinoscopy. Inadequate lymph node sampling was seen in 122 lymph nodes on EBUS-TBNA. Inadequate sampling was generally seen when attempting biopsy of lymph nodes less than 5 mm, and none were subsequently shown to have metastatic cancer at mediastinoscopy or thoracotomy. Ten lymph node stations were thought to have inadequate sampling on mediastinoscopy lacking lymphoid tissue (Table 2).

The lymph node staging based on chest CT, EBUS-TBNA, mediastinoscopy, and final pathology is shown in

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TABLE 1. Patient characteristics

Patient characteristics	n = 153
Age, mean (SD), y	66.8 (9.5)
Gender, no. (%)	
Male	84 (55)
Female	69 (45)
Histology of lung cancer, no. (%)	
Adenocarcinoma	90 (59)
Squamous cell carcinoma	39 (25)
Adenosquamous	2 (1)
Large cell carcinoma	6 (4)
Other types of NSCLC	12 (8)
SCLC	4 (3)
Location of primary tumor, no. (%)	
Right upper lobe	60 (39)
Right middle lobe	7 (5)
Right lower lobe	27 (18)
Left upper lobe	34 (22)
Left lower lobe	25 (16)
Clinical stage, no. (%)	
IA	47 (31)
IB	26 (17)
IIA	3 (2)
IIB	10 (7)
IIIA	59 (39)
IIIB	5 (3)
IV	3 (2)
Nodal stage by CT or PET, no. (%)	
0	90 (59)
1	7 (5)
2	51 (33)
3	5 (3)
Short axis of LN biopsied, mean (SD), mm	
All	6.9 (2.9)
2R	6.7 (2.7)
4R	7.0 (2.9)
2L	3.3 (1.2)
4L	5.6 (2.0)
7	8.1 (3.3)
EBUS time, mean (SD), min	20.2 (8.1)

NSCLC, Non–small cell lung cancer; *SCLC,* small cell lung cancer; *CT,* computed tomography; *PET,* positron emission tomography; *LN,* lymph node; *EBUS,* endobronchial ultrasound; *SD,* standard deviation.

Table 3. The prevalence of N2/N3 disease was 35% (53/153). There was excellent agreement between EBUS-TBNA and mediastinoscopy for mediastinal staging in 136 patients (91%; Kappa, 0.8; 95% CI, 0.7–0.9). Both EBUS-TBNA and mediastinoscopy were incorrect in 4 patients. The 4 patients missed by both EBUS-TBNA and mediastinoscopy had metastases located in station 4R in 1 patient and station 5 or 6 in 3 patients, which were out of reach for EBUS-TBNA and mediastinoscopy. Mediastinoscopy incorrectly staged the mediastinum in 7 patients, and EBUS-TBNA correctly diagnosed these patients with N2 (n = 5) or N3 (n = 2) disease. On the other hand, EBUS-TBNA incorrectly staged 6 patients and

TABLE 2. Lymph node stations biopsied by endobronchial ultrasound-guided transbronchial needle aspiration and mediastinoscopy

LN station	Total	Malignant	Benign	Inadequate
LN stations biopsied by EBUS-TBNA				
2R	30	12	12	6
4R	137	25	74 (5)	38
2L	2	1	0	1
4L	108	15	39 (1)	54
7	149	25	101 (2)	23
Total	426	78	226 (8)	122
LN stations biopsied by mediastinoscopy				
2R	115	16	97 (2)	2
4R	151	26	124 (4)	1
2L	26	1	23	2
4L	132	12	118 (4)	2
7	149	24	122 (4)	3
Total	573	79	484 (14)	10

Number of false-negative LN stations in parentheses. *LN,* Lymph node; *EBUS-TBNA,* endobronchial ultrasound-guided transbronchial needle aspiration.

mediastinoscopy correctly staged these patients with N2 (n = 5) or N3 (n = 1) disease. The 6 patients understaged by EBUS-TBNA included metastases in lymph node stations not sampled by EBUS-TBNA (station 2R) in 2 patients and micrometastases in 4 patients (stations 4R, 4L, 7) (Tables 4 and 5).

The specificity and positive predictive value of both tests were 100%. The sensitivity, negative predictive value, and diagnostic accuracy for mediastinal lymph node staging for EBUS-TBNA and mediastinoscopy were 81%, 91%, 93%, and 79%, 90%, 93%, respectively. There were no significant differences between EBUS-TBNA and mediastinoscopy in yielding the true pathologic N stage (McNemar's test, $P = .78$) (Table 4).

There were no major complications related to EBUS-TBNA or mediastinoscopy. Minor complications from mediastinoscopy were observed in 4 patients (2.6%) (hematoma in 2, left recurrent nerve injury in 1, and wound infection in 1). There were no minor complications related to EBUS-TBNA.

DISCUSSION

The purpose of the present study was to compare the new minimal invasive modality of EBUS-TBNA with the established gold standard of mediastinoscopy for mediastinal lymph node staging of NSCLC. As expected, the specificity

TABLE 3. Lymph node staging based on different modalities

N Stage	CT	EBUS-TBNA	Mediastinoscopy	Final pathology
0	90 (59%)	107 (70%)	109 (71%)	90 (59%)
1	7 (5%)	3 (2%)	N/A	10 (7%)
2	51 (33%)	33 (22%)	35 (23%)	42 (27%)
3	5 (3%)	10 (7%)	9 (6%)	11 (7%)

CT, Computed tomography; *EBUS-TBNA,* endobronchial ultrasound-guided transbronchial needle aspiration.

TABLE 4. Agreement in mediastinal lymph node staging between endobronchial ultrasound-guided transbronchial needle aspiration and mediastinoscopy

EBUS N stage	Mediastinoscopy N stage	Final N stage	No. of cases
Staged correctly by both EBUS and mediastinoscopy			
0 or 1	0 or 1	0 or 1	100
2	2	2	28
3	3	3	8
Staged incorrectly			
0 or 1	0 or 1	2	4
2	0	2	5
3	2	3	2
0	2	2	5
0	3	3	1

The specificity and positive predictive value of both tests were 100%. The sensitivity, negative predictive value, and diagnostic accuracy rate of EBUS-TBNA and mediastinoscopy were 81%, 91%, 93%, and 79%, 90%, 93%, respectively. *EBUS,* Endobronchial ultrasound.

TABLE 5. Patients with false-negative results of mediastinal staging

Patient	Nodal station	Diameter of nodes short/long axis (mm)	Description of case
Staged incorrectly by both EBUS and mediastinoscopy			
1	4R	5/10	4R positive on final pathology
2	6	15/18	6 positive on final surgical staging
3	5	5/5	5, 6 positive on final surgical staging
	6	10/12	
4	5	5/5	5 positive on final surgical staging
Staged incorrectly by EBUS			
1	7	3/8	Micrometastasis
2	4L	3/3	Micrometastasis, not sampled by EBUS
3	2R	3/3	Not sampled by EBUS
4	2R	5/10	N3 lymph node not sampled by EBUS
5	4R	3/8	Micrometastasis
6	7	12/15	Micrometastasis, PET negative
Staged incorrectly by mediastinoscopy			
1	4L	12/18	Enlarged and hard node on mediastinoscopy
2	4L	5/8	Grossly normal on mediastinoscopy
3	4R	15/18	Enlarged node on mediastinoscopy
4	7	5/5	Grossly normal on mediastinoscopy
5	4L	3/5	4R (N2) positive, 4L (N3) negative on mediastinoscopy
6	7	10/12	Grossly normal on mediastinoscopy
7	4L	3/3	2R, 4R (N2) positive, 4L (N3) negative on mediastinoscopy

EBUS, Endobronchial ultrasound; *PET,* positron emission tomography.

and positive predictive value for both techniques, when metastatic cancer was identified, were 100%. The sensitivity, negative predictive value, and diagnostic accuracy for mediastinal lymph node staging for EBUS-TBNA and mediastinoscopy were 81%, 91%, 93%, and 79%, 90%, 93%, respectively. These results demonstrate that these modalities are comparable in that there were no significant differences between EBUS-TBNA and mediastinoscopy in overall ability to determine the true pathologic mediastinal lymph node stage in patients with NSCLC. Both modalities have some limitations, and they are different and in a sense complementary.

EBUS-TBNA is a minimally invasive method of mediastinal biopsy first reported in 2004 with a high diagnostic yield for the evaluation of mediastinal and hilar lymph nodes.[7] As shown by the growing number of publications,[7-18] it is becoming an important modality in the field of interventional pulmonology and thoracic surgery. The advantages of EBUS-TBNA include its (1) minimally invasive nature; (2) real-time targeting of lymph nodes; (3) ability to access hilar, interlobar, and lobar lymph nodes; and (4) safety. Mediastinoscopy has had a long-standing role for the definitive pathologic exclusion of N2 or N3 disease. The current report establishes that EBUS-TBNA can also accurately distinguish N0/N1 disease from N2 and N3 disease. EBUS-TBNA may also provide the possible detection of N1 disease.[14] This will allow future studies to determine whether neoadjuvant chemotherapy could improve survival in subgroups of patients with N1 disease and poor prognosis.[21]

Although mediastinoscopy is reported to have an extremely low complication rate, it requires general anesthesia and may be associated with potentially catastrophic complications, such as bleeding due to injury of major vessels, tracheobronchial injury, and esophageal trauma.[4] Minor complications include left recurrent nerve injury, pneumothorax, and wound infection. In the present study, we did not observe major complications related to mediastinoscopy. Minor complications from mediastinoscopy were observed in 4 patients (2.6%) (hematoma in 2, transient left recurrent nerve injury in 1, and wound infection in 1). There were no complications related to EBUS-TBNA in the present study.

The majority of the patients in the present study had clinical N0 disease on chest CT or PET scan (n = 90, 59%), with a normal mediastinum by CT imaging criteria. This contributes to the sensitivity of 81% in assessing the mediastinum by EBUS-TBNA, because sensitivity is related to the underlying prevalence of N2/N3 disease. Sensitivity in this study is lower than previously reported (85%–96%),[7-18] where EBUS-TBNA was evaluated in the setting of patients with enlarged nodes on CT scan. Although EBUS-TBNA is capable of sampling subcentimeter lymph nodes, there is a limit in sampling very small lymph nodes as shown by the number of inadequate samples in the small sized lymph nodes in the EBUS-TBNA group. We did note that the majority of instances of inadequate sampling by EBUS-TBNA were in lymph nodes less than 5 mm in short axis. It is important to note that none of these inadequate samplings had metastases on final pathology. In our

experience, using current technology, a nodal short axis of less than 5 mm is probably the limit to a good biopsy with the EBUS-TBNA scope and a 22-gauge needle. Sampling errors will always occur in small lymph nodes, which raises the question, do we really need to sample the mediastinum in patients with clinical N0 disease lung cancer with such small lymph nodes? The answer still needs to be further investigated.[22]

Accurate staging remains essential for management of patients with lung cancer. Perhaps the most important issue is the determination of patients who are eligible for curative surgical resection. With the introduction of new modalities, a key issue has been how to incorporate these modalities, such as EBUS-TBNA or EUS-FNA, into the algorithm for lung cancer staging.[6,7] In a recent randomized controlled multicenter trial, a combination of EBUS-TBNA and EUS-FNA followed by mediastinoscopy compared with mediastinoscopy alone resulted in greater sensitivity (from 85% to 94%) for mediastinal lymph node metastases and fewer unnecessary thoracotomies.[23] Our current study did not incorporate EUS-FNA for minimally invasive staging before mediastinoscopy, because the main objective was a direct comparison between 2 procedures (EBUS-TBNA and mediastinoscopy) that have access to the same lymph node stations.

Our current study showed excellent performance of both EBUS-TBNA and mediastinoscopy for identifying patients with negative mediastinal disease with a negative predictive value of 91% and 90%, respectively. The important question is whether one should perform a mediastinoscopy after a negative EBUS-TBNA in potentially resectable lung cancer. The combined sensitivity and negative predictive value of EBUS-TBNA and mediastinoscopy in our current setting were 92% and 96%, respectively. This is only a 5% increase of the negative predictive value for mediastinal staging. In a setting with a low prevalence of mediastinal disease, mediastinoscopy may not add significant advantages after a negative EBUS and may not justify the extra costs.

Study Limitations

Some limitations apply to this study. Because of the study design, EBUS-TBNA was performed under general anesthesia through an endotracheal tube in the majority of cases. This might contribute to the high diagnostic yield in this study compared with awake patients. However, stations 2R and 2L were sometimes difficult to assess because of the presence of the endotracheal tube. The number of sampled lymph nodes at station 2R (EBUS-TBNA 30 nodes vs mediastinoscopy 115 nodes) and 2L (EBUS-TBNA 2 nodes vs mediastinoscopy 26 nodes) indicates the superiority of mediastinoscopy for sampling stations 2R and 2L in our current study protocol. However, we have noted that the use of laryngeal mask airway obviates the limitation imposed by the endotracheal tubes, and we have moved to this form of intubation when performing EBUS-TBNA in an anesthetized patient. This modification might further secure the role of EBUS-TBNA over mediastinoscopy, because 2 of 6 patients in whom EBUS was negative and mediastinoscopy was positive had metastatic disease in station 2.

Second, a cytopathologist was always present for ROSE for EBUS-TBNA. ROSE has been shown to reduce the number of TBNA necessary for a firm diagnosis.[24] Because not all centers have the resources to perform ROSE, the results may not be generalizable to all settings. However, in case of EBUS-TBNA, if one performs 3 passes with the needle for biopsy, there may not be significant differences in the accuracy when performed without ROSE.[12] Real-time imaging of lymph nodes also allows assessment of lymph node morphology that provides an indication of whether a node is normal or not.[15]

Third, EBUS-TBNA was performed by general thoracic surgeons with extensive familiarity with mediastinal anatomy and correlation with radiologic findings. Thus, the excellent results obtained may not be generalizable to all studies of EBUS-TBNA. Nonetheless, this study clearly delineates what can be achieved with this minimally invasive technique under optimal conditions.

Finally, preoperative staging before EBUS-TBNA and mediastinoscopy was mainly based on CT findings, because PET scanning was not available for all patients at the start of the study. CT scanning of the chest is useful in providing anatomic detail, but the accuracy of CT in differentiating benign from malignant lymph nodes in the mediastinum is poor (sensitivity, 51%; 95% CI, 47–54; specificity, 85%; 95% CI, 84–88). PET scanning has improved sensitivity and specificity over CT for staging the mediastinum (sensitivity, 74%; 95% CI, 69–79; specificity, 85%; 95% CI, range 82–88).[25] By combining CT and PET for noninvasive mediastinal lymph node staging, clinical staging would have been altered in our study; however, this does not detract from our primary conclusion that in a head-to-head comparison of EBUS-TBNA and mediastinoscopy, both techniques had equivalent accuracy in the mediastinal staging of lung cancer.

CONCLUSIONS

There were no significant differences between EBUS-TBNA and mediastinoscopy in determining the true pathologic mediastinal lymph node stage in patients with potentially operable lung cancer. These findings have major implications for patients undergoing preoperative staging for lung cancer. Our results show that EBUS-TBNA, when performed as in this study, can replace mediastinoscopy for accurate staging of the mediastinum in potentially resectable lung cancer. Furthermore, EBUS-TBNA avoids an incision, is more comfortable for the patient, and enables

mediastinal reassessment. The potential for repeat sampling with relative ease is also possible with EBUS-TBNA, because redo EBUS-TBNA is simpler and safer than redo mediastinoscopy.[13] Future studies will be needed to evaluate the role of EBUS-TBNA and mediastinoscopy after induction treatment.

Drs Syed M. Quadri and Masaki Anraku from the Division of Thoracic Surgery, Toronto General Hospital, University Health Network, assisted with data collection. The authors thank the data management team at the Division of Thoracic Surgery, Toronto General Hospital, University Health Network (Frances Hui, Jennifer Lister, Judy Horneck) for contributions to the study.

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GTS

Discussion

Dr Joel Cooper *(Philadelphia, Pa)*. I have no disclosures other than great pride in one of my former institutions, the University of Toronto.

Dr Yasufuku, congratulations on your membership this morning to the American Association of Thoracic Surgery. I appreciate the article, which I had a chance to review 1 week in advance, which was outstanding.

I am convinced from the article and your presentation that you have demonstrated equivalent ability to stage the mediastinum with EBUS and mediastinoscopy. It was a well-designed and very well-executed study, and the key features you pointed out were well-trained thoracic surgeons who understand their anatomy, the use of general anesthesia in this particular series, and outstanding cytopathology.

I have several questions I will ask one at a time. Are the results you have presented regarding the correlation between EBUS and mediastinoscopy based on the on-site sampling or were there cases where the cell block and later final pathology changed the results? If you achieved these results with on-site sampling, I want to know how you did it, because we certainly cannot produce this degree of accuracy with on our on-site diagnoses.

Dr Yasufuku. In terms of on-site cytology, we have compared the results of on-site cytologic findings with the final findings from the cell block, and in our 153 patients, there was no discrepancy between the diagnosis of the ROSE cytology and the final cytology. I may not have been clear, but for this study, some patients went directly to resection after the mediastinoscopy and EBUS and then some patients had their resection done a few days later. In case the patient went directly to resection, the decision was based on our findings on ROSE cytology and quick section from lymph nodes sampled by mediastinoscopy.

It is an important issue about whether we can rely on the results of ROSE cytology, and more important to be able to collaborate with your cytopathologists. In our experience, we have learned

a lot by doing this study, because we get direct feedback from the cytopathologist, and by doing that, we have been able to modify how we sample our lymph nodes so that we can submit a better sample.

Dr Cooper. Clearly, the significance that a person attaches to the presence or absence of mediastinal lymph node involvement will determine how vigorously he or she attempts to pursue the goal that you achieved. What is your current policy on patients with known or suspected lung cancer? How important is it to you to obtain accurate mediastinal node sampling before thoracotomy, and what do you do with that information?

Dr Yasufuku. I think accurate mediastinal lymph node staging is an important issue that affects patient outcome. In our current practice, according to the results of our study, when patients have a clinical N2 disease based on imaging, we would start out the invasive staging with endobronchial ultrasound. We not only sample 1 lymph node station, but, as I showed in this study, we typically do systematic lymph node sampling, not just going after 1 lymph node. Even if we do find metastasis in 1 lymph node, we would also check the other mediastinal lymph node stations. If we do confirm the disease and it is resectable, we would have the patient undergo induction treatment. I think the beauty about EBUS is that a redo EBUS is typically easier than a redo mediastinoscopy. So we can go back after induction treatment, follow-up on these patients, and actually safely restage the patients. If necessary, we can always do a mediastinoscopy as well.

Dr Cooper. Thank you, and that answered another question that I had. Finally, do you obtain sufficient material for tumor markers, which increasingly is important in directing the neoadjuvant therapy of these patients?

Dr Yasufuku. Sometimes it may be a challenge, but if done in the correct way, we have been able to obtain adequate samples for molecular analysis, such as epidermal growth factor receptor mutation analysis. Regular immunohistochemistry is done routinely by the cytopathologist using the cell block, and the cytopathologist is typically happy with what we submit.

Dr Frank Detterbeck *(New Haven, Conn)*. Just a quick comment. I think that EBUS is not EBUS is not EBUS, and mediastinoscopy is not mediastinoscopy. Certainly EBUS as you have done it is different from what many people do; they quickly aspirate 1 node station and that is it, and the same with mediastinoscopy, as Alex Little showed us in the United States in 2005, where 50% don't even sample a single node. You have done a very systematic staging. Furthermore, video mediastinoscopy is better than old-fashioned mediastinoscopy. It is important for us to consider these results in this context as we figure out how to implement them more broadly.

Dr Bryan Meyers *(St Louis, Mo)*. I enjoyed your article. It is going to be an excellent contribution to the literature. The only area where either of your treatment arms diverged from standard clinical care was the use of a different needle at each site. Equipment from Olympus was donated for the trial, and so it was okay. We don't have that same advantage during a case of routine clinical care. How do you think that discrepancy might affect the interpretation or generalizability of your results, and could you justify why you chose to do that?

Dr Yasufuku. Thank you for raising an important issue. The reason why we chose to use different needles was because we wanted to eliminate contamination. I think we should ideally use different needles for different lymph node stations, especially when you do not have ROSE cytology where the cytopathologists can tell you if the needle you used was positive for cancer or not. We always start out our sampling from the N3 nodes and then work our way to the N2 and N1 nodes. Needles cost approximately $80 to $100 each, but to prevent contamination and possible upstaging, I think it is important to use different needles.

If you have ROSE cytologic evaluation and the lymph nodes are found to be negative for malignancy, it may be possible to use the same needle after washing the needle properly; however, there have been no studies looking at the use of the same needle for different lymph node stations and the impact on the final diagnosis.

COMMENTARY

Mediastinoscopy: An obsolete procedure?

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Disclosures: Authors has nothing to disclose with regard to commercial support.
Received for publication Sept 28, 2011; accepted for publication Oct 12, 2011.

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J Thorac Cardiovasc Surg 2011;142:1400-2
0022-5223/$36.00

doi:10.1016/j.jtcvs.2011.10.017

For approximately 50 years, mediastinoscopy has been a pivotal part of the pretreatment staging of lung cancer.[1] At one time, respected thoracic surgical groups in North America and Europe considered mediastinoscopy mandatory before proceeding to resection of a non–small cell lung cancer (NSCLC). However, during the past 30 years, improvements in noninvasive imaging modalities, first computed tomography and then positron emission tomography,

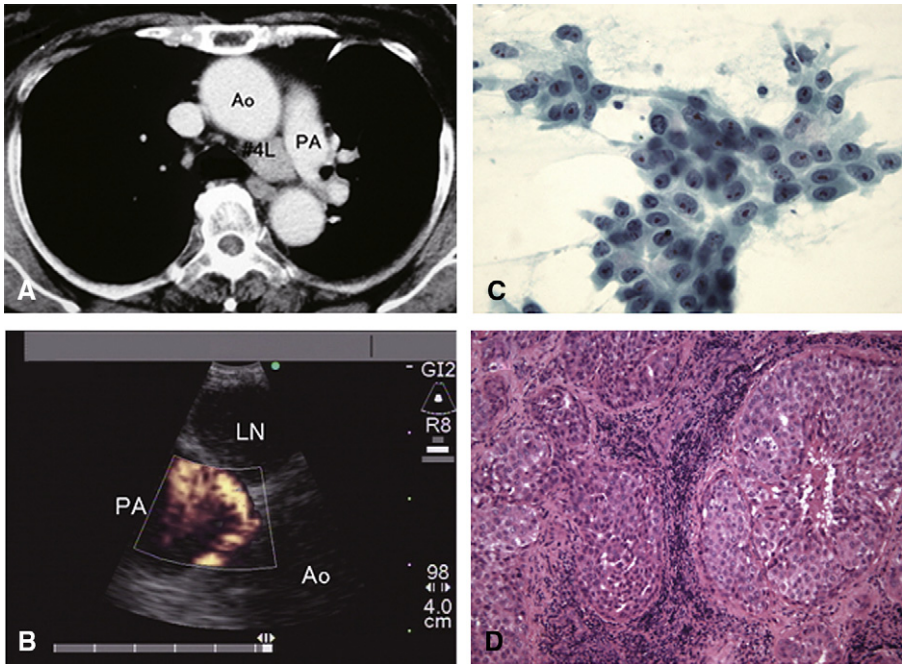

FIGURE E1. A, CT scan demonstrates enlargement of lymph node 4L in 68-year-old patient with lung cancer of the left lower lobe. B, EBUS images with the Doppler mode show 4L (LN) between the aorta and the pulmonary artery. Cytologic and pathologic results demonstrate adenocarcinoma (C, D). *AO,* Aorta; *PA,* pulmonary artery; *LN,* lymph node.