Diagnosis of Mediastinal Adenopathy—Real-Time Endobronchial Ultrasound Guided Needle Aspiration versus Mediastinoscopy

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Background: Real-time endobronchial ultrasound has increased the accuracy of conventional transbronchial needle aspiration biopsy in sampling mediastinal lymph nodes. Nevertheless, direct comparisons with mediastinoscopy are not available to determine the role of endobronchial ultrasound in pathologic staging.

Objectives: To compare the diagnostic yield of endobronchial ultrasound against cervical mediastinoscopy in the diagnosis and staging of radiologically enlarged mediastinal lymph nodes stations accessible by both modalities in patients with suspected nonsmall cell lung cancer.

Methods: Prospective, crossover trial with surgical lymph node dissection used as the accepted standard. Biopsy results of paratracheal and subcarinal lymph nodes were compared.

Results: Sixty-six patients with a mean age 60 ± 10 years were studied. The prevalence of malignancy was 89% (59/66 cases). Endobronchial ultrasound had a higher overall diagnostic yield (91%) compared with mediastinoscopy (78%; $p = 0.007$) in the per lymph node analysis. There was disagreement in the yield between the two procedures in the subcarinal lymph nodes (24%; $p = 0.011$). There were no significant differences in the yield at other lymph node stations. The sensitivity, specificity, and negative predictive value of endobronchial ultrasound were 87, 100, and 78%, respectively. The sensitivity, specificity, and negative predictive value of mediastinoscopy were 68, 100, and 59%, respectively. No significant differences were found between endobronchial ultrasound (93%) and mediastinoscopy (82%; $p = 0.083$) in determining true pathologic N stage (per patient analysis).

Conclusions: In suspected nonsmall cell lung cancer, endobronchial ultrasound may be preferred in the histologic sampling of paratracheal and subcarinal mediastinal adenopathy because the diagnostic yield can surpass mediastinoscopy.

Key Words: Endobronchial ultrasound, Cervical mediastinoscopy, Nonsmall cell lung cancer, Transbronchial needle aspiration, Mediastinal lymph nodes.

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Accurate staging of the mediastinum is essential to evaluate prognosis in nonsmall cell lung cancer and to devise an appropriate treatment plan. The poor sensitivity and specificity of noninvasive radiologic techniques make histologic staging indispensable in patients who are potential candidates for surgical resection.[1,2] The overall sensitivity of transbronchial needle aspiration (TBNA) in invasive staging is 78% with a range of 14 to 100%.[2] Endobronchial ultrasound (EBUS) with a radial probe has an improved TBNA diagnostic yield of 71 to 85%.[3–7] Real-time EBUS with a linear probe has pushed the positive yields further into the 86 to 100% range.[8–16] The two components of successful diagnostic yield are true positives from a definite histologic result and true negatives that either need further confirmatory tests or adequate clinical follow-up. The ability to obtain a definitive histologic diagnosis through real-time EBUS-TBNA ranges from 24 to 94% and is largely dependent on the prevalence of malignancy in the study population.[9–16] This has resulted in doubts over the negative predictive value of EBUS-TBNA results. The recommendations stating that negative conventional TBNA results should be verified with a mediastinoscopy may therefore also hold true for real-time EBUS-TBNA.[2]

Although mediastinoscopy is regarded as the accepted standard in the diagnosis of pathologic mediastinal lymph nodes, the reported sensitivity is 78% with a range of 40 to 92%.[2] Standard cervical mediastinoscopy has access limited to paratracheal (station 2 and 4) and subcarinal (station 7) lymph nodes. No direct evaluation has been made with other invasive staging modalities and historical comparisons have selection biases based on differing lymph node sizes, lymph node stations, locally available expertise and risks of the staging modality used. The specificity of mediastinoscopy is

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reported to be 100% but this has also never been confirmed against surgical lymph node dissection.[2]

A prospective, crossover trial was conducted to compare the diagnostic yields of real-time EBUS-TBNA against cervical mediastinoscopy in patients with mediastinal adenopathy and suspected nonsmall cell lung cancer. Systematic lymph node dissection during surgical tumor resection was used as our reference accepted standard to address the issue of specificity.

METHODS

Consecutive subjects who had clinically suspected nonsmall cell lung cancer were enrolled between January 2005 and July 2006. Clinical suspicion was based on age, symptoms, and risk factors such as smoking history and computed tomography (CT) characteristics. Inclusion criteria required technically resectable pulmonary lesions in patients fit for operation with no clinical/radiologic evidence of T4 disease or distant metastases. Positron emission tomography (PET) was not used and histology was unconfirmed at time of enrollment. Therefore, confirmation of diagnosis and staging proceeded concurrently. Mediastinal adenopathy (≥10 mm) on CT had to be confined to lymph node stations 2, 4 or 7 to qualify for inclusion. Patients with lymphadenopathy at other mediastinal lymph node stations were excluded because these lymph nodes were inaccessible by either standard cervical mediastinoscopy or EBUS. The Institutional Review Boards of the participating centers approved the data collection and analysis.

Mediastinoscopy

Cervical mediastinoscopy was performed on all patients and was used as the standard of care in making treatment decisions such as operation. Lymph node sampling of all station 2, 4, and 7 nodes was done.

Real-Time EBUS-TBNA

EBUS evaluation was incorporated into the preoperative airway inspection of the patients. EBUS was performed either as separate procedure under moderate sedation and within 1 week before mediastinoscopy or concurrently at the time of medistinoscopy under general anesthesia. Only pathologically enlarged lymph nodes identified on CT scans were biopsied.

After airway examination with conventional bronchoscopy, EBUS-TBNA was performed using the real-time ultrasound biopsy bronchoscope (XBF-UC260F-OL8; Olympus Ltd, Tokyo, Japan). A 7.5 Hz linear ultrasound transducer with a maximum penetration of 50 mm is linked to the EU-60 processor (Olympus Ltd, Tokyo, Japan). TBNA biopsies were performed using a dedicated 22-gauge needle (XNA-202, Olympus Ltd, Tokyo, Japan; Figure 1).

Lymph nodes were identified by slow withdrawal and rotation of the ultrasound transducer. Intervening vessels were avoided by using the integrated Doppler function. The jabbing method was used to obtain biopsies and two passes were made at each lymph node station. The aspirate was placed on four glass slides, air-dried, and stained. No rapid on-site cytologic evaluation was used. If multiple lymph node stations were biopsied, a different needle was used for each station after flushing the working channel with normal saline.

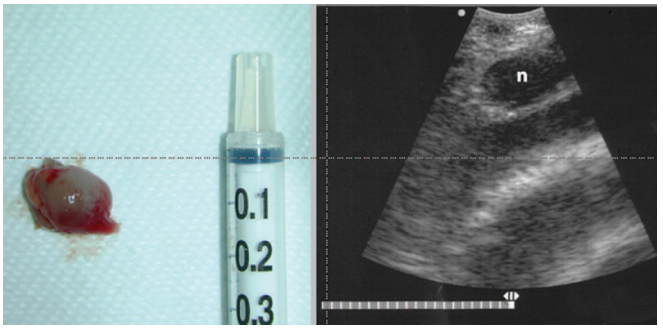

FIGURE 1. The ultrasound image shows the clear delineation of a small lymph node (n) during endobronchial ultrasound guided TBNA. On the left the same lymph node after resection. The puncture mark is visible as a red mark on the left corner of the node.

Surgery

Patients who had negative mediastinal evaluations by both EBUS-TBNA and mediastinoscopy underwent surgical resection and systematic lymph node dissections. Nonsmall cell lung cancer cases confirmed by either procedure were also offered operation in instances of limited stage 3A disease with single station N2 disease and no evidence of extracapsular spread on mediastinoscopy on protocol.

End-Points

Primary outcome was comparative diagnostic yields of EBUS-TBNA and cervical mediastinoscopy in the evaluation of lymph nodes that were enlarged on CT scans. Diagnostic yields incorporated both true positive and true negative results. The ability of either procedure to establish a specific histologic diagnosis was a secondary objective. Agreement between EBUS-TBNA and mediastinoscopy was also evaluated. Safety was assessed by recording all complications.

Data Analysis

Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, North Carolina, USA). Continuous variables are expressed using mean and standard deviation. Categorical variables are summarized as counts and percents. Comparisons of continuous variables were done with Student's t tests. χ^2 test or Fisher's exact test, as appropriate was used for comparing proportions. McNemar's test was used for evaluating agreement between the two procedures. Generalized estimating equations were used for multivariate analysis of yield using the covariates of lymph node station and histology. A two-tailed p value of <0.05 indicated statistical significance.

RESULTS

Eighty-five patients were identified as possible subjects after review by the multidisciplinary tumor boards. Nineteen patients could not be enrolled, as they either refused consent ($n = 17$) of were deemed unfit for anesthesia ($n = 2$). Sixty-six patients met inclusion criteria and were enrolled and 120 enlarged mediastinal lymph nodes (mean lymph nodes per patient: 1.8 ± 0.1 with a range of 1–4) were biopsied by both EBUS-

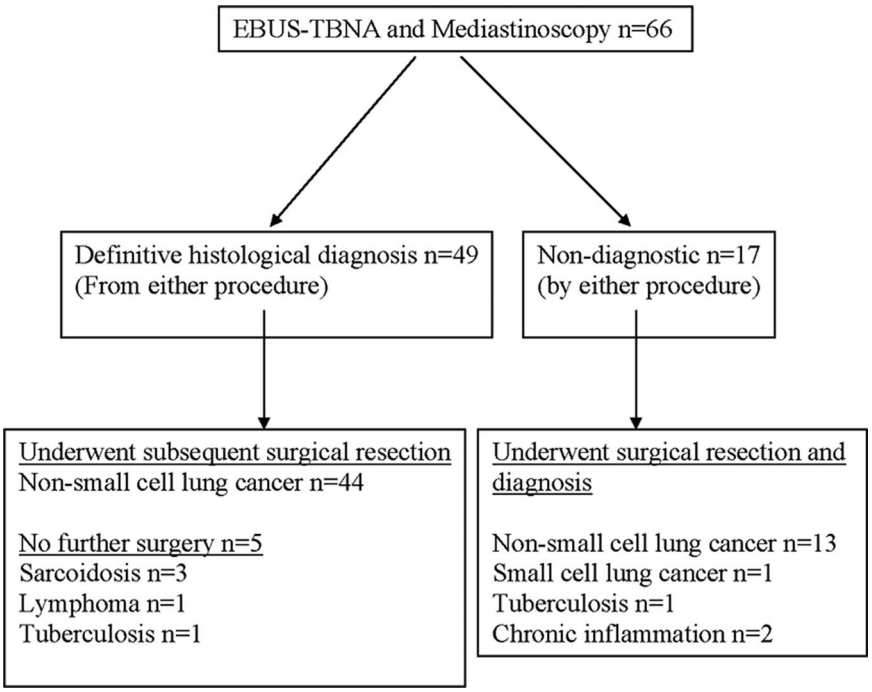

FIGURE 2. Patient flow and final histologic diagnosis.

TBNA and mediastinoscopy. Operation was performed by eight different surgeons and EBUS TBNA was performed by three different endoscopists. The patients' mean age was 60 ± 10 years and 29/66 (44%) were females. The prevalence of malignancy was 59/66 (89%). Of these 59 patients, there were 57 cases of nonsmall cell lung cancer, one case of small cell lung cancer and one case of lymphoma. There were seven patients with benign disease: three cases of sarcoidosis, two pulmonary tuberculosis, and two nonspecific inflammation.

A definitive histologic diagnosis was established by either EBUS-TBNA or mediastinoscopy in 49 (49/66; 74%) patients before operation (Figure 2). Operation was performed for either therapeutic or diagnostic indications in 61 (61/66; 92%) patients. Therefore, the sensitivity and specificity of EBUS-TBNA and mediastinoscopy was compared against operation as the accepted standard in 112 (112/120; 93%) lymph nodes. Five patients who did not undergo operation (three sarcoidosis, one lymphoma, and one tuberculosis) had eight (8/120; 7%) enlarged mediastinal lymph nodes. Definitive histology was available on all eight lymph nodes from either EBUS-TBNA or mediastinoscopy and was considered the accepted standard in these patients.

Diagnostic Yield

The 120 lymph nodes that were sampled had a mean size of 15 ± 2.6 mm; range: 10 to 21 mm. The diagnostic yield in a per lymph node analysis of EBUS-TBNA (109/120; 91%) was higher than the yield of mediastinoscopy (94/120;

TABLE 1. Diagnostic Yield of EBUS-TBNA and Mediastinoscopy in the Evaluation of Mediastinal Lymph Nodes

	Lymph Node Size in mm: Mean ± SD (Range)	EBUS Yield (%)	Mediastinoscopy Yield (%)	p^a
All lymph nodes	15 ± 2.6 (10–21)	109/120 (91)	94/120 (78)	0.007
Lymph node station				
2 all	16 ± 3.1 (10–21)	24/25 (96)	22/25 (88)	0.30
2 right	18 ± 1.6 (14–20)	12/13 (92)	11/13 (85)	0.99
2 left	14 ± 3.6 (10–21)	12/12 (100)	11/12 (92)	0.99
4 all	15 ± 2.6 (10–19)	45/54 (83)	40/54 (74)	0.24
4 right	15 ± 2.6 (10–19)	29/34 (85)	24/34 (71)	0.14
4 left	15 ± 2.6 (10–19)	16/20 (80)	16/20 (80)	0.99
7	15 ± 2.4 (10–19)	40/41 (98)	32/41 (78)	0.007
Pathology				
Malignant	16 ± 2.7 (10–21)	64/74 (86)	49/74 (66)	0.004
Benign	15 ± 2.5 (10–21)	45/46 (98)	45/46 (98)	0.99

[a] χ^2 test.

78%; $p = 0.007$). A higher accuracy of EBUS-TBNA in the subcarinal lymph node station was observed (Table 1). The diagnostic rates from the paratracheal lymph node stations were not different between the two procedures. The lymph node sizes in the various lymph node stations were similar and there was no significant difference in size between malignant (16 ± 2.7 mm) and benign lymph nodes (15 ± 2.5 mm; $p = 0.14$). The diagnostic yield of EBUS-TBNA was also higher among the malignant lymph nodes (86 versus 66%; $p = 0.004$).

In multivariate analysis, real-time EBUS-TBNA had a higher diagnostic yield than mediastinoscopy ($p = 0.005$). However, there was no statistical significant interaction between lymph node station and malignant/benign histology ($p = 0.395$).

The sensitivity of real-time EBUS-TBNA was 71/82 (87%) and specificity was 38/38 (100%). The prevalence of malignancy in all the lymph nodes biopsied was 74/120 (62%) and the negative predictive value of EBUS-TBNA was 38/49 (78%). The sensitivity, specificity, and negative predictive value of mediastinoscopy was 56/82 (68%), 38/38 (100%), and 38/64 (59%), respectively.

In a per patient analysis, the overall diagnostic yield of EBUS-TBNA was 59/66 (89%) and the yield of mediastinoscopy was 52/66 (79%; $p = 0.1$). In the 57 patients with nonsmall cell lung cancer, the correct pathologic N stage was predicted in 53/57 (93%) with EBUS-TBNA and in 47/57 (82%) with mediastinoscopy ($p = 0.083$).

In obtaining a definite histologic diagnosis, there was trend towards a better result with EBUS-TBNA (59%) compared with mediastinoscopy (47%) but this did not reach statistical significance ($p = 0.05$). This trend towards an improved diagnostic result was also seen in the subcarinal lymph node station (Table 2).

The overall agreement between the diagnostic yields of EBUS-TBNA and mediastinoscopy was 78%. Significant

TABLE 2. Definite Histological Diagnosis from EBUS-TBNA and Mediastinoscopy in the Evaluation of Mediastinal Lymph Nodes

	Lymph Node Size in mm: Mean ± SD (Range)	Positive EBUS (%)	Positive Mediastinoscopy (%)	p^a
All lymph nodes	15 ± 2.6 (10–21)	71/120 (59)	56/120 (47)	0.05
Lymph node station				
2 all	16 ± 3.1 (10–21)	13/25 (52)	11/25 (44)	0.57
2 right	18 ± 1.6 (14–20)	8/13 (62)	7/13 (54)	0.69
2 left	14 ± 3.6 (10–21)	5/12 (42)	4/12 (33)	0.99
4 all	15 ± 2.6 (10–19)	32/54 (59)	27/54 (50)	0.33
4 right	15 ± 2.6 (10–19)	20/34 (59)	15/34 (44)	0.23
4 left	15 ± 2.6 (10–19)	12/20 (60)	12/20 (60)	0.99
7	15 ± 2.4 (10–19)	26/41 (63)	18/41 (44)	0.08
Pathology				
Malignant	16 ± 2.7 (10–21)	64/74 (86)	49/74 (66)	0.004
Benign	15 ± 2.5 (10–21)	7/46 (15)	7/46 (15)	0.99

[a] χ^2 test.

TABLE 3. Agreement in Definite Histological Diagnosis between EBUS-TBNA and Mediastinoscopy in the Evaluation of Mediastinal Lymph Nodes

		Disagreement (%)		
	Overall Agreement (%)	+EBUS/−MED	−EBUS/+MED	p^a
All lymph nodes	93/120 (78)	21/120 (18)	6/120 (5)	0.004[b]
Lymph node station				
2 all	23/25 (92)	2/25 (8)	0/25 (0)	0.16
2 right	12/13 (92)	1/13 (8)	0/13 (0)	0.32
2 left	11/12 (92)	1/12 (8)	0/12 (0)	0.32
4 all	39/54 (72)	10/54 (19)	5/54 (9)	0.20
4 right	25/34 (74)	7/34 (21)	2/34 (6)	0.10
4 left	14/20 (70)	3/20 (15)	3/20 (15)	1.00
7	31/41 (76)	9/41 (22)	1/41 (2)	0.011
Pathology				
Malignant	47/74 (64)	21/74 (28)	6/74 (8)	0.004
Benign	46/46 (100)	0/46 (0)	0/46 (0)	—

[a] McNemar's test.
MED, mediastinoscopy.

disagreement between the two procedures was found in the subcarinal station and in lymph nodes with evidence of malignant metastases (Table 3). Analysis of the cases where there was disagreement revealed that there were more cases when EBUS-TBNA resulted in definitive diagnosis and mediastinoscopy was negative (18%) compared with when mediastinoscopy yielded a positive diagnosis and EBUS-TBNA was negative (5%; $p = 0.004$).

The overall diagnostic yield of combining EBUS-TBNA and mediastinoscopy was 115/120 (96%). This was not significantly higher than the 91% yield of EBUS alone ($p = 0.20$). The five nondiagnostic lymph node biopsies by both EBUS-TBNA and medaistinoscopy occurred in four patients. In two patients (Stations 4R and 4L), the diagnosis was established in biopsy of other lymph node stations by either procedure. The other two patients had tuberculosis (Station 4R) and nonsmall cell cancer (Station 2R and 4R) respectively diagnosed on surgical biopsy. One further patient had negative biopsies of lymph node stations 2L, 4L, and 7. These were confirmed as true negatives on operation. Nevertheless, surgical excision biopsy of the primary lung lesion yielded a diagnosis of small cell lung cancer. Therefore, combined EBUS-TBNA and mediastinoscopy yielded an accurate result in 63 (63/66; 95%) patients.

Safety

There were no complications observed with EBUS-TBNA. Among patients who underwent mediastinoscopy, there were two cases of postoperative wound infection and three instances of prolonged bleeding. One other patient required pro-longed ventilation (≥24 hours). Nevertheless, as mediastinoscopy was performed before lung resection in a combined setting, it was difficult to attribute complications specifically to mediastinoscopy.

DISCUSSION

In patients who have suspected nonsmall cell cancer with enlarged paratracheal and subcarinal lymph nodes, the diagnostic yield of real-time EBUS-TBNA was superior to the yield of cervical mediastinoscopy. The two procedures were comparable in ability to establish a definitive histologic diagnosis and in correctly predicting the pathologic N stage with the trend in favor of EBUS-TBNA. These findings may be unexpected given that biopsy specimens from mediastinoscopy are obtained under direct vision and are considerably larger than those from the 22-guage EBUS-TBNA needle. Nevertheless, the limited sensitivity of mediastinoscopy in prior studies has been largely attributed to metastases in lymph nodes not accessible by the mediastinoscope.[2] Posterior subcarinal nodes are one such lymph node group that is beyond the reach of mediastinoscopy and this may explain the improved yield of EBUS-TBNA at station 7 and the consequent superior overall diagnostic rate. At the paratracheal lymph node stations 2 and 4, the results of EBUS-TBNA and mediastinoscopy were not significantly different.

The high diagnostic yield of EBUS-TBNA is attributed to real-time visualization of the needle tract in the ultrasound plane during biopsy of lymph nodes. EBUS also may prevent rare complications associated with conventional TBNA such as inadvertent vascular and mediastinal injury. Cervical mediastinoscopy has a relatively higher complication rate with mortality reported between 0.08 and 0.2% and a morbidity rate of 2% and 2.5%.[2,17,18] Often reported complications include arrthymias, bleeding, and injury to adjacent structures such as the trachea, esophagus, and recurrent laryngeal nerve.[17,18] EBUS is also an outpatient procedure that can be performed under moderate sedation. Prior data suggest no difference in the diagnostic rate between EBUS performed under general anesthesia and under moderate sedation.[12]

EBUS-TBNA can be easily repeated without the technical difficulties and increased complication rates encountered with repeat mediastinoscopy.[19] Furthermore, EBUS has access to N1 lymph node stations beyond the reach of mediastinoscopy and can also be combined with transesophageal ultrasound to sample the aortopulmonary (station 5), paraesophageal (station 8), and inferior pulmonary ligament (station 9) nodes to accomplish complete endoscopic staging of the mediastinum.[6,20]

Although our findings have suggested the role of EBUS-TBNA as the preferred procedure in diagnosing enlarged paratracheal and subcarinal lymph nodes in suspected nonsmall cell lung cancer, mediastinoscopy clearly retains an important role. The role of invasive staging in a radiologically normal mediastinum remains controversial and in our study mediastinoscopy was used to exclude contra lateral lymph node metastases before proceeding with operation.[21] Although there is emerging data on the utility of EBUS-TBNA in the staging of such nonenlarged mediastinal lymph nodes, no study with direct comparison against mediastinoscopy has been performed yet.[14] Mediastinoscopy also provides the surgeon with important preoperative data such as evidence of lymph node extracapsular extension and mediastinal invasion of tumor.[22] The utility of EBUS-TBNA outside the scope of suspected nonsmall cell lung cancer is also increasing. Recent data in patients with a high clinical suspicion of sarcoidosis has shown a diagnostic yield of 85–86% with EBUS-TBNA.[15,23] Nevertheless, more data is needed with direct comparisons against mediastinoscopy before negative EBUS-TBNA results can be trusted in patients where the pretest probability of nonsmall cell lung cancer is low.

The increasing evidence of the accuracy of EBUS-TBNA in diagnosing mediastinal adenopathy with suspected lung cancer has paved the way forward for greater collaboration between the endoscopist and the thoracic surgeon. EBUS-TBNA is less invasive, safer, and possibly more accurate. It can be considered a first line procedure when diagnosis and staging proceed in parallel for patients with a clinically presumed diagnosis of nonsmall cell lung cancer who also have radiologic evidence of mediastinal adenopathy. Attempting to confirm negative EBUS-TBNA findings with mediastinoscopy should be reconsidered because there is limited additional yield in combining EBUS-TBNA with mediastinoscopy. Nevertheless, in patients with surgically resectable tumors, there remains a role for preoperative mediastinoscopy to assess local mediastinal invasion and to exclude metastases in nonenlarged lymph nodes. This collaborative paradigm will potentially achieve a

less invasive and more satisfying histologic staging of the mediastinum in lung cancer.

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