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Original Article

The Diagnostic Utility of Real-Time EBUS-TBNA for Hilar and Mediastinal Lymph Nodes in Conventional TBNA Negative Patients

Erdoğan Çetinkaya, MD,[1] M. Akif Özgül, MD,[1] Nuri Tutar, MD,[2] Güler Özgül, MD,[3] Ertan Çam, MD,[1] and Semra Bilaçeroğlu, MD[4]

Background: There are many causes of mediastinal and hilar lymphadenopathy, such as neoplasms, granulomatous diseases, infections and reactive hyperplasia. Nowadays, the popularity of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is increasing in the diagnosis of mediastinal and hilar lymphadenopathy. We aimed to investigate the diagnostic value of EBUS-TBNA in patients with mediastinal and/or hilar lymphadenopathy and previously conventional TBNA-negative or inadequate results.
Methods: Retrospective analysis was performed in 64 patients with previously conventional TBNA- negative or inadequate results and consequently undergoing EBUS-TBNA between July 2007 and August 2011.
Results: One hundred and twenty three lymph nodes were sampled by EBUS-TBNA in 64 patients with no complications. In the 63 (98.4%) cases with adequate results, the sensitivity, diagnostic accuracy, and NPV of EBUS-TBNA per patient was 90.5%, 90.6%, and 66.6%, respectively. In a total of 122 (99.1%) adequately sampled lymph nodes, the diagnostic sensitivity, accuracy, and NPV of EBUS-TBNA per nodal station were 87.8%, 90.1%, and 65.7%, respectively. Non-small cell lung cancer (NSCLC) (n = 21, 33.3%) and sarcoidosis (n = 16, 25.3%) were the most common malignant and benign diseases in the patients with adequate samples by EBUS-TBNA. The relationships of diagnostic accuracy with the number of lymph nodes sampled, number of passes per node, or size of lymph nodes were both insignificant ($p > 0.05$).
Conclusion: EBUS-TBNA is a sensitive and accurate method for the assessment of mediastinal and hilar lymph nodes in patients with conventional TBNA negative results.

Keywords: bronchoscopy and interventional techniques, lung cancer, histology/cytology

[1]*Department of Pulmonary Medicine, Yedikule Chest Disease and Surgery Training and Research Hospital, Istanbul, Turkey*
[2]*Department of Pulmonary Medicine, Erciyes University School of Medicine, Kayseri, Turkey*
[3]*Department of Pulmonary Medicine, Bağcılar Training and Research Hospital, Istanbul, Turkey*
[4]*Department of Pulmonary Medicine, Izmir Training and Research Hospital for Thoracic Medicine and Surgery, Izmir, Turkey*

Received: June 5, 2012; Accepted: September 4, 2012
Corresponding author: Nuri Tutar, MD. Department of Pulmonary Medicine, Erciyes University School of Medicine, Kayseri 38038, Turkey
Email: drnuritutar@gmail.com

Introduction

There are many causes of mediastinal and hilar lymphadenopathy, such as neoplasms, granulomatous diseases, infections and reactive hyperplasia.[1)] Multiple modalities are available for sampling mediastinal and hilar lymph nodes. These range from minimally invasive approaches, such as conventional transbronchial needle aspiration, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic esophageal ultrasound-guided fine needle aspiration (EUS-FNA) and computed tomography (CT)-guided percutaneous needle aspiration to surgical approaches, such

as mediastinoscopy, mediastinotomy, and thoracoscopy.[2] In these procedures, mediastinoscopy has been the gold standard in the diagnosis and staging of enlarged mediastinal lymph nodes, but it is invasive, expensive, and requires general anesthesia.[3,4]

Transbronchial needle aspiration (TBNA) is a minimally invasive bronchoscopic procedure for diagnosing mediastinal and hilar lymphadenopathy. However, conventional TBNA relies on conventional needle puncture guided only by CT scans or positron emission tomography/computed tomography (PET/CT) and it is not real-time. Furthermore, it was reported that only about 10% of pulmonologists performed TBNA routinely for diagnosing or staging malignant diseases.[5]

Nowadays, the popularity of EBUS-TBNA is increasing worldwide. A convex-probe (CP) EBUS allows real-time imaging under direct US guidance. This makes it easier to locate the lymph nodes to be sampled. In their study, Yasufuku, et al. reported that EBUS-TBNA had a sensitivity of 94.6%, specificity of 100% and diagnostic accuracy rate of 96.3%, which seemed to be superior to mediastinoscopy or conventional TBNA.[6] In addition, the procedure is uneventful without complications.

In the present study, we aimed to investigate the diagnostic value of real-time CP EBUS-TBNA in patients with mediastinal and/or hilar lymphadenopathy identified by CT and/or PET-CT. All of these patients had conventional TBNA-negative or inadequate results, previously.

Methods

Patients

Between July 2007 and August 2011, 858 patients underwent endobronchial ultrasound studies for a variety of clinical indications at the Yedikule Training and Research Hospital, in Istanbul, Turkey. We retrospectively analyzed the data of 68 patients who had a negative or inadequate sample obtained by conventional TBNA previously. These patients underwent EBUS-TBNA according to lymph node short axis on CT (>1 cm) or increased F-18 fluorodeoxyglucose uptake on PET/CT (compared with surrounding tissues). conventional TBNAs were performed by different bronchoscopists and at different hospitals, but EBUS-TBNAs were performed by the same bronchoscopist, EÇ. Four patients were excluded owing to insufficient data or follow-up so 64 patients were eventually included in the study. The study was approved by the Scientific Study Committee of Yedikule Chest Disease and Surgery Training and Research Hospital.

EBUS-TBNA Procedure

CP EBUS was conducted using a fiberoptic ultrasound bronchoscope (BF-UC 160F-OL8; Olympus Medical Systems, Tokyo, Japan). The location, shape, and structure of the lesions were examined by ultrasound. Lymph node stations were named and numbered using the lymph node map proposed by Mountain.[7] The bronchoscope was guided to the lesion. During real-time imaging, 22-gauge aspirating needle with syringe model NA-201SX-4022 (Olympus), manufactured for this purpose, was pushed out from the distal tip of the bronchoscope and samples consisting of cells or tissue fragments were obtained. The aspirate was smeared onto glass slides, air dried, fixed immediately with 95% alcohol, and stained with Hematoxylin and Eosin (HE). Histological cores were fixed with 10% neutral buffered formalin and stained with HE. Immunohistochemical staining was also performed when considered necessary. Rapid onsite cytopathological examination (ROSE) was not performed.

Definitions

Cytopathological specimens were categorized as (i) *malignant sample*, showing the presence of malignant cells, (ii) *benign sample*, consisting of mature lymphocytes, granulomas with necrosis and neutrophils or without necrosis, (iii) *non-classified*; inadequate sample showing absence of lymphocytes, or reactive sample consisting of mature lymphocytes but without malignant cells or granulomas. Patients who were diagnosed with anthracosis or non-classified by EBUS-TBNA subsequently underwent mediastinoscopy or had clinical and radiological follow-up for at least 6 months

Statistical Analysis

Descriptive statistics are presented as frequency, percentage, median, minimum and maximum values. The diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of EBUS-TBNA were calculated by standard definitions. The chi-square test was performed to assess the diagnostic accuracy of EBUS-TBNA in lymph nodes of different size (a cut-off lymph node diameter of 20 mm was arbitrarily assigned), in number of lymph nodes

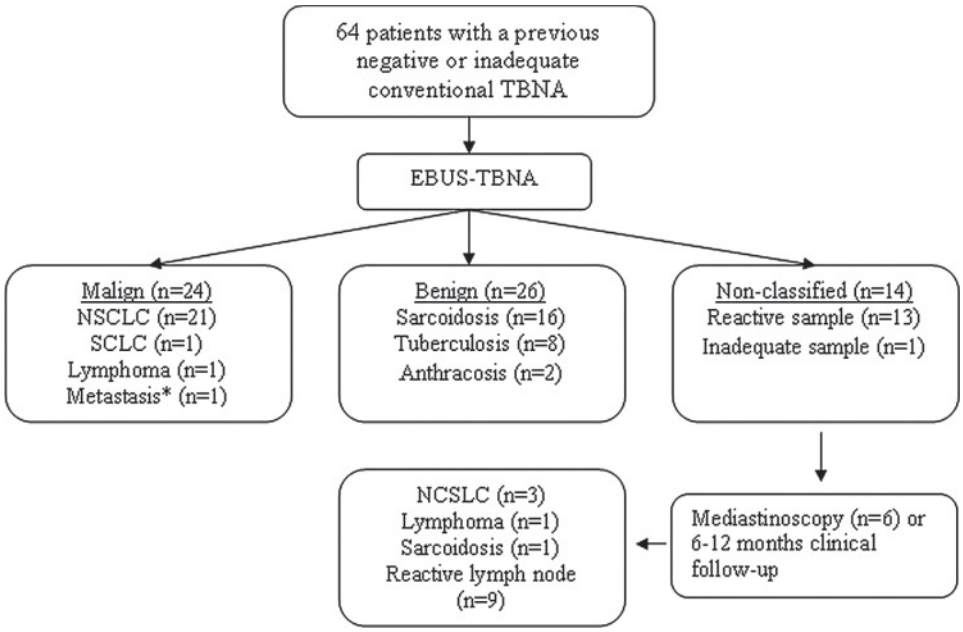

Fig. 1 Flowchart of patients.

Table 1 Characteristics of patients and lymph nodes

Patient characteristics	
Number of patients, n	64
Male/female, n	49/15
Age, years*	54.5 (21–89)
Lymph node characteristics	
Number lymph nodes, n	123
Node size, mm*	16 (6.8–45)
Number of lymph nodes sampled*	2 (1–4)
Number of passes*	2 (1–6)

* Data represent median (range).

sampled and in number of passes per node. A p value of less than 0.05 was considered to be significant. The data were entered into a database and analyzed with the SPSS statistical software package (SPSS 15.0, Chicago, Illinois, USA).

Results

Real-time CP EBUS-TBNA was performed on 64 conventional TBNA-negative patients. All of the patients underwent EBUS-TBNA because of their first diagnosis. There were 49 male and 15 female patients, with a median age of 54.5 (range 21–89) years. One hundred and twenty three nodes were sampled in 64 patients. The median size of the lymph nodes seen at EBUS-TBNA was 16 mm (range 6.8–45 mm) and each node underwent a median of 2 (range 1–6) passes. The median number of lymph nodes sampled was 2 (range 1–4). There were no serious complications related to EBUS-TBNA. The characteristics of the patients and lymph nodes are shown in (**Table 1**).

The conventional TBNA showed inadequate specimens in 15 (23.4%) patients, and non-diagnostic specimens in 49 (76.6%) patients. (**Fig. 1**) presents the flow chart for the patients included in the study. The specimen was inadequate by EBUS-TBNA in only 1 (1.5%) patient. Of the 63 patients with adequate samples, 50 (79.3%) were positive and 13 (20.6%) negative by EBUS-TBNA. In the 50 with positive results, EBUS-TBNA showed malignancy in 24 (38.0%): non-small cell lung cancer (NSCLC) in 21 (33.3%), small cell lung cancer (SCLC) in 1 (1.5%), mediastinal metastases from extrathoracic malignancy in 1 (1.5%) and lymphoma in 1 (1.5%). Twenty-six patients (41.2%) were diagnosed with benign diseases by EBUS-TBNA. Sarcoidosis (n = 16, 25.3%) was the most common benign disease in the patients with adequate samples by EBUS-TBNA. Tuberculosis and anthracosis were also diagnosed by EBUS-TBNA in 8 (12.6%) and 2 cases (3.1%), respectively. In the remaining 13 negative cases (20.6%), the EBUS-TBNA specimens showed reactive lymph node. In the patients with EBUS-TBNA specimens being inadequate or showing anthracosis or reactive lymph node, mediastinoscopy (6 patients) or a clinical and radiological

Table 2 Diagnostic Performances of EBUS-TBNA

Parameters	No (%)
Based on no. of patients	64
Adequacy of samples	63/64 (98.4)
Sensitivity	48/53 (90.5)
Specificity	10/10 (100)
Positive predictive value	48/48 (100)
Negative predictive value	10/15 (66.6)
Diagnostic accuracy	58/63 (90.6)
Based on number of lymph nodes	123
Adequacy of samples	122/123 (99.1)
Sensitivity	87/99 (87.8)
Specificity	23/23 (100)
Positive predictive value	87/87 (100)
Negative predictive value	23/35 (65.7)
Diagnostic accuracy	110/122 (90.1)

EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration

follow-up (10 patients) was performed for a median of 10 mo (6–12 mo). NSCLC (n = 3), lymphoma (n = 1), sarcoidosis (n = 1) and reactive lymph node (n = 1) were diagnosed by mediastinoscopy. The EBUS-TBNA results of these six patients were reactive (n = 5) or inadequate samples (n = 1). Patients who were found to have NSCLC, lymphoma and sarcoidosis by mediastinoscopy were recorded as false negative results by EBUS-TBNA. The patient with an inadequate sample by EBUS-TBNA was found to have a reactive lymph node by mediastinoscopy. Nine patients with reactive lymph nodes and two patients with anthracosis did not have any treatment, remain well, and there was no change in the size of their lymph nodes during the follow-up period.

The diagnostic performances of EBUS-TBNA are shown in **Table 2**. In the 63 (98.4%) cases with adequate results, the sensitivity, diagnostic accuracy, and NPV of EBUS-TBNA per patient were 90.5%, 90.6%, and 66.6%, respectively. In the 122 (99.1%) adequately sampled lymph nodes, the diagnostic sensitivity, accuracy, and NPV of EBUS-TBNA per nodal station were 87.8%, 90.1%, and 65.7%, respectively. The diagnostic accuracy of EBUS-TBNA on a disease basis was 87.5% (21/24) in NSCLC, 100% (1/1) in SCLC, 50% (1/2) in lymphoma, 94.1% (16/17) in sarcoidosis, 100% (8/8) in tuberculosis, and 100% (2/2) in anthracosis.

The characteristics of hiler and mediastinal lymph nodes and diagnostic yields assessed by EBUS-TBNA are shown in **Table 3**. In the sampled 123 lymph nodes, the specimen was inadequate in only 1 (0.8%) with the station in the left upper paratracheal lymph node. The subcarinal lymph node station (n = 38, 30.9%) and right lower paratracheal lymph node station (n = 30, 24.4%) were the most aspirated sites in the present study. EBUS-TBNA had the lowest sensitivity (66.6%) for the left lower paratracheal lymph node station. However, its diagnostic accuracy, which was higher than its sensitivity, was 85.7%. Additionally, the sensitivity and diagnostic accuracy of EBUS-TBNA were 86.4% and 88.6% in hilar and interlobar lymph nodes right and left together, respectively.

The number of sampled lymph nodes, number of passes per node and lymph node size were compared in EBUS-TBNA-positive and –negative patients. The relationships of diagnostic accuracy with number of sampled lymph nodes (n ≤1 or n >1) or with number of passes per node (n ≤1 or n >1) were both insignificant (p >0.05). The relationship of diagnostic accuracy and size of lymph nodes (<20 mm or ≥20 mm) was also statistically insignificant (p >0.05).

Discussion

The present study confirms that with overall sensitivity and diagnostic accuracy of 90.5% and 90.6%, respectively, real-time CP EBUS-TBNA is a sensitive and accurate procedure for the assessment of mediastinal and hilar lymph nodes in patients with conventional TBNA-negative results.

In the past, patients with conventional TBNA negative results underwent mediastinoscopy to clarify the etiology of mediastinal lymph node enlargement. However, nowadays EBUS-TBNA has become a procedure that should be performed before mediastinoscopy in patients with negative conventional TBNAs. Although these three procedures have several advantages over each other in different perspectives, EBUS-TBNA seems to be superior.

Conventional TBNA is a cost-effective procedure for the sampling of mediastinal and hilar lymph nodes.[8] However, the yield for conventional TBNA varies widely from 20% to 89% in the pertinent literature, and seems to be related to the size and location of the lesion, as well as to operator's experience.[5,9–11] Herth, et al. compared EBUS-TBNA versus conventional TBNA by dividing patients into two groups, namely subcarinal or all other stations.[12] In the subcarinal group, the yield of conventional TBNA was 74% compared to 86% in the EBUS group (difference not significant). However, in the other stations, the overall yields for EBUS-TBNA

Table 3 Characteristics of 123 lymph nodes sampled by EBUS-TBNA

Characteristics	True positive	True negative	False negative	Inadequate	Total no (%)	Sensitivity*	Diagnostic Accuracy*
Lymph node							
2R	1	0	0	0	1 (0.8)	100%	100%
2L	1	1	0	1	3 (2.4)	100%	100%
4R	23	4	3	0	30 (24.4)	88.4%	90%
4L	2	4	1	0	7 (5.7)	66.6%	85.7%
7	29	6	3	0	38 (30.9)	90.6%	92.1%
10R or 11R	14	3	0	0	17 (13.8)	100%	100%
10L or 11L	17	5	5	0	27 (22.0)	77.2%	81.4%

*Data calculated in adequate samples. R: right; L: left; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration

and conventional TBNA were 84% and 58%, respectively, and this difference was highly significant.

Mediastinoscopy is considered as the gold standard for the histologic evaluation of mediastinal lymph nodes with a sensitivity ranging from 86% to 94%.[13,14] It can only sample nodal stations 1–4 and 7, cannot access hilar nodal stations and has a morbidity of 1% and mortality of 0.05% which increases with inexperienced hands.[4,15]

In contrast, the EBUS-TBNA procedure is safe and minimally invasive, and does not require general anesthesia or hospitalization.[16] The complication rate is extremely low, and it has access to all of the mediastinal lymph node stations accessible by mediastinoscopy as well as N1 nodes with an overall diagnostic accuracy of 92.6% and sensitivity of 90%.[16,17] In the current study, 122 (99.1%) lymph nodes were adequately sampled with no complications by EBUS-TBNA. Based on the number of nodes, the overall diagnostic accuracy and sensitivity were 90.1% and 87.8%, respectively. Furthermore, the diagnostic accuracy was 88.6% and sensitivity 86.4% in hilar or interlobar lymph nodes, which was similar to those in pertinent literature.

The diagnostic yield of EBUS-TBNA in granulomatous diseases was previously reported. EBUS-TBNA had a diagnostic yield of 79%–100% in tuberculosis[18–21] and 33%–93.8% in sarcoidosis.[18,19,22,23] Tremblay, et al. compared EBUS-TBNA with 22-gauge needle and conventional TBNA with a 19-gauge needle in sarcoidosis.[22] They reported that the diagnostic yield was 53.8% vs 83.3% in favor of the EBUS-TBNA group with a significant increase of 29.5% in the yield. In the present study, the diagnostic accuracy of EBUS-TBNA in patients with tuberculosis and sarcoidosis were 100% and 95.1%, respectively which were comparable to those in other studies.

Our finding of a reduction in sensitivity in left lower paratracheal (66.6%) and left hilar or interlober lymph nodes (77.2%) is in contrast to the earlier reports of EBUS-TBNA in sampling mediastinal and hilar lymph nodes.[16,18] The comparatively smaller lymph node sizes and true negative results in these stations may have influenced this finding. However, it is important to note that the left paratracheal area is a difficult area for both conventional or EBUS-TBNA. This may be another reason for this lower sensitivity.

During EBUS-TBNA, real-time imaging is provided to sample lymph nodes and this is superior to conventional bronchoscopy. It should be noted that the commonly used 22-gauge cytologic needle length is 13 mm for conventional bronchoscopy. A 21-gauge and 15 mm long needle can be used for conventional TBNA to increase diagnostic accuracy. However, for EBUS-TBNA, a 22-gauge and 40 mm needle is used and it allows sampling of lymph nodes from one end to the other. Probably, this is another reason for why EBUS-TBNA is a more diagnostic procedure than conventional TBNA.

The relationship between diagnostic accuracy and number of needle passes or size of lymph nodes was reported previously. Ye, et al. reported that there was no significant association between the diagnostic accuracy of EBUS-TBNA and number of needle passes or size of lymph nodes in 101 patients in whom 225 lymph nodes were sampled.[24] In a recent Italian case series, the diagnostic yield of EBUS-TBNA and size of lymph nodes did not show significant relation in 100 lymph nodes sampled.[25] Similarly, in the present study the diagnostic accuracy of EBUS-TBNA was higher if >1 node was sampled, >1 pass was made or node size was ≥20 mm but the difference was not significant. Theoretically, the diagnostic accuracy of EBUS-TBNA should be significantly higher when the node size is larger or number of

passes or nodes is greater but this is not so in practice. These results suggest that neither the size of lymph nodes nor the number of passes or nodes are key factors in determining the diagnostic accuracy of EBUS-TBNA.

However, whether EBUS-TBNA can be applied as the first-line procedure for diagnosis of mediastinal lymphadenopathy is still controversial, because of its negative predictive value of 11%–97.4%.[23,26] Also, Gurioli, et al. reported the NPV was 64.7% in patients with lymphadenopathies/masses with diameters less than 2.5 cm or with a previous negative conventional TBNA.[25] Similarly, NPVs on a patient basis and on a nodal station basis were 66.6% and 65.7% in the present study, respectively. These results show that further investigation is required in patients with negative EBUS-TBNA results.

The present study had several limitations. It was retrospective in design and included a relatively small number of patients. Secondly, conventional TBNA procedures were not performed by the same bronchoscopist. Additionally, hilar or interlobar lymph nodes were not recorded separately.

In conclusion, real-time CP EBUS-TBNA is a minimally invasive and accurate procedure for assessing conventional TBNA-negative mediastinal and hilar lymph nodes. However, it should be kept in mind that if EBUS-TBNA is negative, further diagnostic procedures, such as mediastinoscopy, are required to reveal the etiology of enlarged mediastinal/hilar lymphadenopathy.

Disclosure Statement

There is no conflict of interest regarding to this manuscript.

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