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The diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration as an initial diagnostic tool

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Background/Aims: Real-time, convex probe endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is used for the staging of malig-nant mediastinal lymph nodes. We evaluated the diagnostic efficacy and safety of EBUS-TBNA when used as an initial diagnostic tool.

Methods: We retrospectively studied 56 patients who underwent EBUS-TBNA as an initial diagnostic tool between August 2010 and December 2011. Procedure purpose were classified into four categories: 1) intrathoracic masses adjacent to the central airway; 2) enlarged lymph nodes for concurrent diagnosis and staging in suspected malignancy; 3) enlarged lymph nodes in suspected malignancy cases with inability to perform percutaneous core needle biopsy (PCNB); and 4) solely mediastinal masses/lymph nodes in lieu of mediastinoscopy.

Results: The diagnostic accuracy of EBUS-TBNA regardless of procedure purpose was calculated to be 83.9%. Furthermore, the diagnostic accuracy of malignant disease was significantly higher than benign disease (93.9% vs. 70.6%, $p < 0.001$). The diagnostic accuracy of EBUS-TBNA for each disease is as follows: tuberculo-sis, 50%; sarcoidosis, 60%; aspergillosis, 100%; lung abscess, 100%; lung cancer, 93%; and lymphoma, 100%. There were minor complications in seven patients during the EBUS-TBNA procedure. The complications included mild hypoxia and bleeding.

Conclusions: In conclusion, EBUS-TBNA is a useful initial diagnostic tool for both benign and malignant diseases. EBUS-TBAN is also a very safe procedure and less invasive compared to mediastinoscopy or PCNB.

Keywords: Endobronchial ultrasound-guided transbronchial needle aspiration; Mediastinal mass; Intrathoracic mass

INTRODUCTION

Lung cancer continues to account for a significant portion of new cancer diagnoses each year. Surgery remains the most effective treatment, with the excep-tion of small cell lung cancer, for which systemic che-motherapy is recommended. If lung cancer is suspected during a screening visit, a histopathological examination is necessary to identify the anatomical stage of the ma-lignancy and evaluate the possibility of surgical exci-sion [1]. Mediastinal lymph nodes (LNs) are typically ex-amined using mediastinoscopy and transbronchial

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needle aspiration (TBNA) cytology, but general anesthesia use during mediastinoscopy and the diagnostic accuracy of TBNA are ongoing challenges. More recently, real-time convex probe endobronchial ultrasound-guided TBNA (EBUS-TBNA) has been introduced as a novel method to concurrently target the suspected lesion and obtain the specimen [2-5]. Studies have found that EBUS-TBNA was not diagnostically inferior to procedural examinations such as transbronchial lung biopsy, bronchoalveolar lavage, or radiological examinations such as positron emission tomography (PET) [6-9]. However, few studies have reported the use of EBUS-TBNA as both an initial diagnostic tool for benign and malignant diseases and as a tool for staging of malignant tumors [10]. Furthermore, to our knowledge, no study has investigated the diagnostic value of EBUS-TBNA in specific situations. Thus, in this study, we evaluated the diagnostic efficacy and safety of EBUS-TBNA as an initial diagnostic tool.

METHODS

Study design and participants
This study was conducted from August 2010 to December 2011 at Chungbuk National University Hospital (Cheongju, Korea). We enrolled patients > 18 years of age who presented with an intrathoracic mass and/or mediastinal lymphadenopathy on chest computed tomography (CT). Written, informed consent was obtained from all subjects and this study was approved by the Ethics Review Committee of Chungbuk National University Hospital.

Intervention
A chest CT scan was performed on all patients, and a PET scan was performed in cases of suspected malignancy. The presumptive diagnoses were based on the patient's clinical features, laboratory results, and radiological findings. Benign etiologies included tuberculosis and sarcoidosis; malignant diseases included lung cancer, malignancy of unknown origin (MUO), and lymphoma.

EBUS-TBNA was performed by a single pulmonologist in the bronchoscopy suite on all patients. Patients were instructed to fast for at least 4 hours prior to the procedure. A 1% lidocaine solution was used as a topical anesthesia, and conscious sedation was achieved by intermittent intravenous midazolam injection. Heart rate and oxygen saturation were monitored in real-time. All of the patients underwent TBNA via flexible ultrasound-guided bronchoscope with a linear scanning probe on the tip (BF-UC 260F-OL8, Olympus Medical Systems, Tokyo, Japan). When target lesions (masses/LNs) were visualized, punctures were created by a 22-gauge needle (NA-201SX-4022, Olympus Medical Systems) with the help of real-time imaging. Any complications, such as hypotension, arrhythmia, hypoxia, and bleeding, were recorded throughout the procedure. Because a pathologist was not present for rapid on-site evaluation, it was not possible to evaluate whether the biopsy specimens were sufficient; therefore, we tried to obtain at least two biopsy specimens or three cytological specimens, on the basis of a study conducted by Lee et al. [8]. Pathological examination of the specimens was conducted in the hospital Department of Pathology. If the biopsy results were inconclusive, patients underwent invasive diagnostic procedures, such as percutaneous core needle biopsy (PCNB), mediastinoscopy, or thoracoscopy to collect additional specimens. For each procedure, data was collected regarding the number of specimens, number of punctures, specimen type (cytology or biopsy), as well as the lesion size on CT by measuring the long-axis diameter of a mass and the short-axis diameter of a LN.

The indications of EBUS-TBNA were also reviewed and classified into four major categories: 1) lesion adjacent to the central airway (e.g., TBNA was performed instead of PCNB or thoracoscopy); 2) simultaneous diagnosis and staging (e.g., in patients suspected of having advanced lung cancer with mediastinal lymphadenopathy, TBNA was used for one-step mediastinal lymphadenopathy instead of sequential lung mass and mediastinal biopsies); 3) inability to perform PCNB (e.g., the lesions were located adjacent to a large vessel such as the aorta or the lesion was too small for PCNB); and 4) replacement of mediastinoscopy (e.g., the lesions were located only in the mediastinum) (Fig. 1). For each category, the diagnostic accuracy, sensitivity, specificity, positive predictive value, and nega-

tive predictive value were calculated.

Statistical analysis

The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated using standard formulations. Descriptive statistical analyses were performed using the SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA) and Spearman test. A $p < 0.05$ was considered to indicate statistical significance.

RESULTS

We evaluated 81 cases of EBUS-TBNA during the study period, and excluded 25 patients prediagnosed with lung cancer undergoing staging work-ups. We included 56 patients (Fig. 2), and the characteristics of whom are summarized in Table 1. Of these patients, 40 (71.4%) were male. The mean age was 68 ± 15.1 years (range, 22 to 87). The presumptive diagnoses were based on clinical features and imaging findings: be-
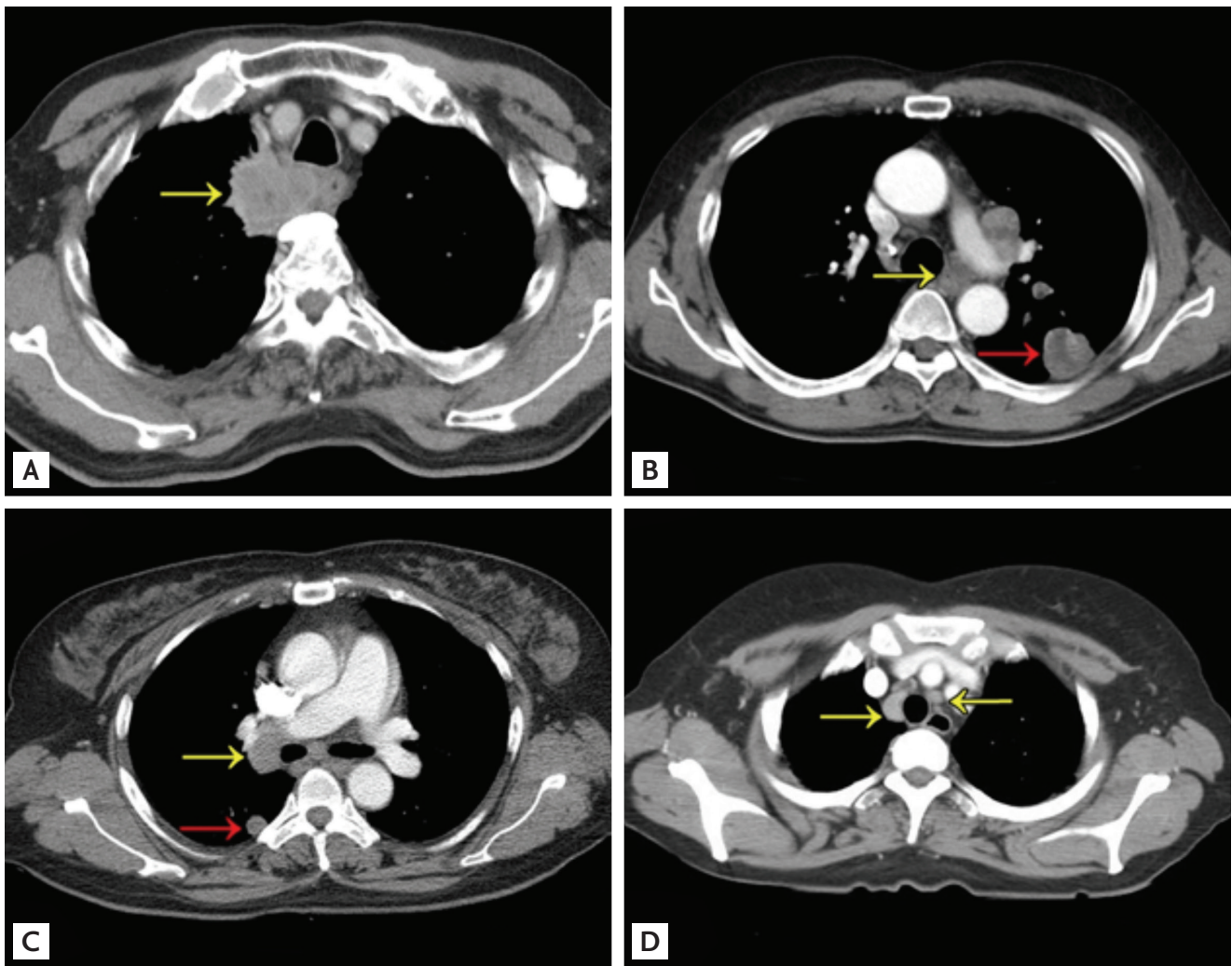

Figure 1. (A) A chest computed tomography (CT) scan reveals a large paratracheal mass (yellow arrow). Transbronchial needle aspiration was recommended instead of percutaneous core needle biopsy (PCNB). (B) Simultaneous diagnosis and staging of a suspected primary lesion (red arrow) by CT scan. PCNB was recommended due to accessibility issues. The CT scan also revealed a lesion suspicious for mediastinal lymph node (LN) metastasis (yellow arrow). (C) CT scan reveals a small-sized nodule in the right lower lobe (RLL) of the lung (red arrow) and LN enlargement in the right Hilar area (yellow arrow). The RLL nodule is too small for PCNB. (D) CT scan reveals LN enlargement only at the anterior/posterior window (yellow arrows), and so mediastinoscopy is recommended.
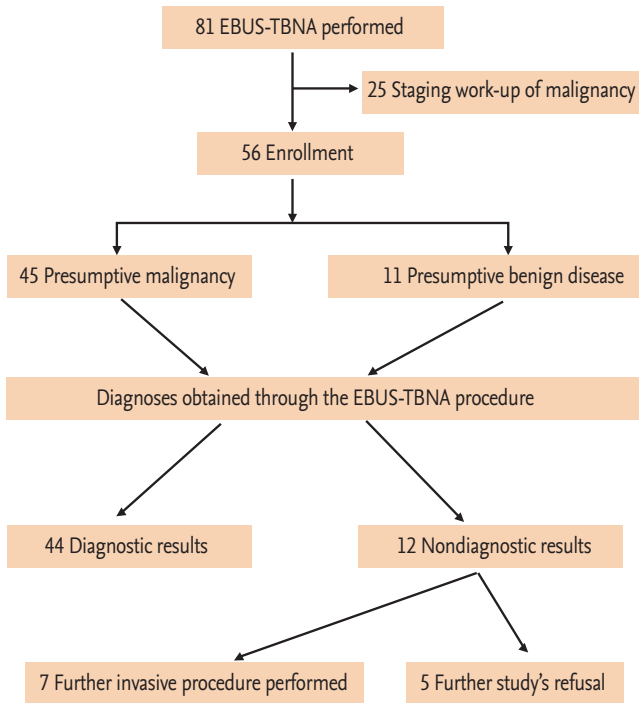
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Figure 2. Flow diagram of patient enrollment, diagnostic procedures, and results. EBUS-TBNA, endobronchial ultrasound guided transbronchial needle aspiration.

Table 1. Clinical characteristics of patients

Characteristic	Value
Total patients (males/females)	56 (40/16)
Median age, yr	68 (22–87)
Presumptive diagnosis	
Lung cancer	33 (59)
MUO	7 (12)
Tuberculosis	7 (12)
Lymphoma	5 (9)
Sarcoidosis	4 (8)
The purpose of EBUS-TBNA	
Lesions adjacent to central airway	9 (16)
Concurrent diagnosis and staging work-up	22 (39)
Inability to perform PCNB	8 (15)
Replacement of mediastinoscopy	17 (30)
Median size of lesion of CT, mm	22 (9–35)
Median no. of puncture	3 (2–4)
Median no. of obtained specimens	2 (1–4)
Diagnosed patients by EBUS-TBNA	44 (79)
The type of diagnosed specimens	
Both biopsy and cytology	30 (68)
Biopsy only	14 (32)
Cytology only	0 (0)
Final diagnosis	
Lung cancer	31 (70)
Lung abscess	4 (9)
Tuberculosis	3 (7)
Sarcoidosis	3 (7)
Aspergillosis	2 (5)
Lymphoma	1 (2)

Values are presented as number (%) or median (range).
MUO, malignancy of unknown origin; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; PCNB, percutaneous core needle biopsy, CT, computed tomography.

nign disease was diagnosed in significantly fewer patients (11 patients, 19.6%) than malignant disease (45 patients, 80.5%; $p < 0.01$). Tuberculosis accounted for seven (63.6%) and sarcoidosis accounted for four (36.4%) of the benign diagnoses. Lung cancer accounted for the highest proportion of the malignant diseased (n = 33, 73.3%), followed by MUO (n = 7, 15.6%), and lymphoma (n = 5, 11.1%). Lesions adjacent to the central airway were present in nine cases (16%). Concurrent diagnoses and staging work-ups were performed in 22 cases (39%), inability to perform PCNB occurred in eight cases (15%), and 17 cases (30%) were replacement procedure for mediastinoscopy.

The median size of target lesions was 22 mm (range, 9 to 35) on CT. The median number of punctures performed was three, and the median number of specimens obtained per patient was two. Both cytological and biopsy specimens were obtained in 53 cases (94.6%), only cytological specimens were obtained in three cases (5.4%). The EBUS-TBNA procedure resulted in a diagnosis in 44 patients (79%). The diagnoses were made with both cytological and biopsy speci-

mens in 30 cases (68%), and were made from only biopsy specimens in 14 cases (32%). There were no diagnoses in all three cases from which only cytological specimens were obtained. Seven of the nondiagnosed patients underwent more invasive procedures including mediastinoscopy (five patients) and video-assisted thoracic surgery (two patients) for diagnosis. They were eventually diagnosed with tuberculosis (n = 3),

sarcoidosis (n = 2), and lung cancer (n = 2). Of the initially nondiagnosed patients, five did not undergo the next diagnostic procedure because they refused further evaluation (n = 3) or transferred to another hospital (n = 2).

Diagnoses made using EBUS-TBNA included lung cancer (n = 31, 70%), lung abscess (n = 4, 9%), tuberculosis (n = 3, 7%), sarcoidosis (n = 3, 7%), aspergillosis (n = 2, 5%), and lymphoma (n = 1, 2%). The all-diagnostic accuracy of EBUS-TBNA, regardless of procedure purpose, was calculated as 83.9%. Furthermore, the diagnostic accuracy of malignant disease was significantly higher than benign disease (93.9% vs. 70.6%, $p < 0.001$). The diagnostic accuracy of EBUS-TBNA for each disease was as follows: tuberculosis, 50%; sarcoidosis, 60%; aspergillosis, 100%; lung abscess, 100%; lung cancer, 93%; and lymphoma, 100% (Table 2). The diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for each EBUS-TBNA indication are shown in Table 3.

Minor complications occurred in seven patients during the EBUS-TBNA procedure. The complications were mild hypoxia (n = 4, 7.1%) and minor bleeding (n = 3, 5.3%) (Table 4). These complications did not require additional procedures or modification of treatment plans. No deaths resulted from the procedure.

DISCUSSION

TBNA with a flexible bronchoscope is a well-established technique used to obtain samples from the sub-

Table 2. Diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle aspiration biopsy according to disease

Diagnosis	Final diagnosis[a]	Initial diagnosis[b]
Benign diseases	17	12 (70.6)
Tuberculosis	6	3 (50)
Sarcoidosis	5	3 (60)
Aspergillosis	2	2 (100)
Lung abscess	4	4 (100)
Malignant diseases	34	32 (94.1)
Lung cancer	33	31 (93.9)
Lymphoma	1	1 (100)
Total	51	44 (83.9)

Values are presented as number or number (%).
[a]Final diagnoses obtained after procedures include endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and invasive modalities.
[b]Initial diagnoses obtained after convex probe-EBUS-TBNA.

Table 3. Diagnostic value of endobronchial ultrasound-guided transbronchial needle aspiration according to indication

Indication	Accuracy	Sensitivity	Specificity	PPV	NPV
Lesion adjacent to central airway (A)	88.9	88.9	-	100	0
Concurrent diagnosis and staging (B)	81.9	85.7	100	100	25
Inability to perform PCNB	75	100	100	100	100
Replacement of mediastinoscopy	70.6	80	100	100	40
Total	79.1	88.7	100	100	41.3

Values are presented as percentage.
PPV, positive predictive value; NPV, negative predictive value; PCNB, percutaneous core needle biopsy.

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Table 4. Adverse events associated with the endobronchial ultrasound-guided transbronchial needle aspiration procedure

Type	No. (%)
Fatal AE	
Death	0/56 (0)
Arrhythmia	0/56 (0)
Nonfatal AE	
Hypoxia	4/56 (7.1)
Minor bleeding	3/56 (5.3)
Total	7/56 (12.5)

AE, adverse event.

carinal and right paratracheal areas, but its diagnostic accuracy is unsatisfactory [11,12]. Although EBUS-TBNA use has been increasing in Korea, it is used primarily to evaluate the mediastinal LNs for the staging of lung cancer or to perform a mediastinal lymphadenopathy instead of a mediastinoscopy under general anesthesia.

EBUS-TBNA is useful in several other clinical settings for the diagnosis of intrapulmonary and mediastinal tumors, and adenopathies of unknown etiology, such as sarcoidosis and lymphoma [13,14]. Few studies have investigated the initial diagnostic accuracy of EBUS-TBNA according to the suspected disease, including benign and malignant etiologies [10]. Furthermore, the value of EBUS-TBNA in concurrent diagnosis and staging without primary biopsy has not been evaluated.

In this study, patients were presumptively diagnosed based on their clinical presentation (general symptoms such as pain and weight loss) and respiratory symptoms (e.g., cough, sputum, and fever), as well as laboratory results and radiological findings. However, presumptive diagnoses were limited by the ambiguity of symptoms and possible atypical presentations of diseases. EBUS-TBNA provided adequate specimen collection for diagnosis in 44 of 56 patients (78.6%), consistent with previous reports [15,16]. Insufficient specimens were obtained from 12 patients and further invasive methods were used for the diagnosis in seven patients. Diagnostic consistency of benign diseases was observed in 12 of 17 cases (70.6%), while diagnostic

consistency of malignant disease was observed in 32 of 34 cases (94.1%). The results were consistent with those reported in previous studies [17].

All four indications were highly accurate in diagnosis, but there were significant differences in the diagnostic accuracy and negative predictive value for each. Furthermore, unlike other previous studies, we performed EBUS-TBNA for only mediastinal lymphadenopathy without PCNB in suspected advanced lung cancer. Eighteen patients were diagnosed using this single procedure without PCNB. Interestingly, only EBUS-TBNA specimens provided enough tissue for genetic analysis, as well as diagnosis, in eight lung adenocarcinoma patients. Considering the above results, we carefully suggest that concurrent diagnosis and staging could decrease the duration of hospitalization, medical expenses, and complications caused by invasive procedures, compared to the evaluation process routinely used in advanced lung cancer patients.

There are several contraindications for EBUS-TBNA. Most contraindications to flexible bronchoscopy are related to the potential for tachycardia, bronchospasm, or hypoxemia. Absolute contraindications include current or recent myocardial ischemia, poorly controlled heart failure, and exacerbation of asthma or chronic obstructive pulmonary disease. Relative contraindications are related to bleeding risk. Minor complications of EBUS-TBNA include agitation, cough, and blood at the puncture site. Studies on EBUS-TBNA of peripheral pulmonary nodules reported moderate bleeding in 1% and pneumothorax in < 4% of cases [18-20]. In this study, mild hypoxia (n = 4, 7.1%) and minor bleeding (n = 3, 5.3%) occurred during some procedures, but there were no severe complications.

The limitations of the study must be acknowledged. First, it was conducted retrospectively, and hence, the data are limited to the information available. Second, a relatively small number of patients were included in this study. Finally, all examinations were conducted by only one pulmonologist. EBUS-TBNA is a comparatively recent technique, and few suites are allocated for its use. Thus, the skill level varies depending upon the operator and his/her experience. Because of the above limitations, we know that our findings are difficult to generalize. We expect that a multicenter, large-scale, prospective study will commence as soon as possible,

focusing on concurrent diagnosis and staging of lung cancer patients.

In conclusion, EBUS-guided TBNA is a useful initial diagnostic tool for both benign and malignant diseases. In addition, it is safer and less invasive than mediastinoscopy or PCNB.

KEY MESSAGE

1. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a useful intial diagnostic tools as well as staging workup in lung cancer patients.
2. The diagnostic yiels of malignant disease is more higher than benign disease.
3. EBUS-TBNA is very safe procdure.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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