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# Efficiency of EBUS-TBNA for diagnosing benign and malignant lymphadenopathy

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ABSTRACT

**Objective**: To determine whether endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can rapidly distinguish among lung cancer, tuberculosis and sarcodosis, and to explore its sensitivity and specificity. **Methods:** Clinical data of patients with enlarged mediastinal or hilar lymphadenopathy who underwent EBUS-TBNA at our hospital between September 1, 2012 and June 30, 2015 for were retrospectively analyzed. The sensitivity, specificity, positive predictive value, and negative predicted value [including 95% confidence interval (*CI*)] were calculated.. **Results:** A total of 299 lymph nodes from 201 patients underwent EBUS-TBNA were selected and no serious complications occurred. EBUS-TBNA showed a sensitivity of 87.9% (124/141) (95% *CI*: 81%–92%), a specificity of 100.0% (124/124) (95% *CI*: 97%–100%), and a negative predicted value of 41.3% (95% *CI*: 23%–61%) in the detection of lung cancer. The sensitivity and specificity of diagnosis of mediastinal tuberculosis lymphadenitis were 72.4% (21/29) (95% *CI*: 53%–87%) and 100.0% (95% *CI*: 82%–100%); while sensitivity and specificity of diagnosis of sarcoidosis were 71.4% (5/7) (95% *CI*: 29%–96%) and 100.0% (95% *CI*: 91%–100%). **Conclusions**: The sensitivity and specificity of EBUS-TBNA do not significantly differ for a diagnosis of lung cancer versus tuberculosis or sarcodosis.

## 1. Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a new and minimally invasive technique. It has been reported that EBUS-TBNA is equivalent or superior to mediastinoscopy in evaluating mediastinal adenopathy of patients with lung cancer[1]. EBUS-TBNA has also been found to be safe and highly useful cytologic and histologic sampling method. Furthermore, EBUS-TBNA can provide visualization of the parabronchial structure to precisely locate peripheral lung lesions, and then to increase diagnostic rate[2].

A pooled analysis showed 90% sensitivity of EBUS-TBNA as detecting mediastinal nodal metastases among 1 299 patients with known or suspected non-small cell lung cancer[3]. Another study including 65 patients showed 85.0%–91.8% sensitivity of EBUS-TBNA for the detection of sarcoidosis[4]. However, there have been

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fewer studies on rapid diagnosis of mediastinal lymphadenopathy secondary to lymphoma, tuberculosis (TB), and other benign diseases by EBUS-TBNA[5,6]. Moreover, there have been no studies published comparing the role of EBUS-TBNA in diagnosing malignant versus benign mediastinal lymphadenopathy. Therefore, we explored the role of EBUS-TBNA in assessing patient with suspected malignant or benign mediastinal lymphadenopathy to compare the sensitivity and specificity of EBUS-TBNA.

## 2. Materials and methods

### 2.1. Patients

All of the patients with enlarged mediastinal or hilar lymphadenopathy who underwent EBUS-TBNA and visited our hopistal between September 1, 2012 and June 30, 2015 were included in this study. A retrospective analysis was performed after the completion of treatment and it was approved by the institutional review board of Sun Yat-Sen University with informed consent.

Baseline diagnostic evaluation was performed for every patient and it included clinical history, physical examination, chest radiograph, computed tomography (CT) of the chest, and the following laboratory tests: tuberculin skin test, complete blood count, coagulation profile, liver and renal function tests, angiotensin-converting enzyme levels, and HIV serology. When chest CT scan showed short axis diameter of a lymph node$\geqslant$10 mm or positron emission tomography/CT scan showed fluorodeoxyglucose uptake of a lymph node was increased compared with surrounding tissue regardless of size, it was regarded as thoracic lymph node by EBUS-TBNA. Patients with pregnancy or a history of a uncorrected bleeding disorder were excluded.

### 2.2. EBUS-TBNA

Before EBUS-TBNA, all patients were nebulized with a 2% lidocaine solution. A topical 2% lidocaine gel was then applied in the nasal cavity and 2% lidocaine was applied over the vocal cords and airways. Intravenous sedation was not performed before or during the bronchoscopy. Oxygenation was monitored as for a standard bronchoscopy. A standard conventional, flexible bronchoscope (BF-UC260F-OL8, Olympus, Tokyo, Japan) was initially used to examine the tracheobronchial tree. Patients received EBUS-TBNA in supine position *via* transnasal (or oral) route. Any abnormalities in the bronchial tree (*e.g.* erythema, plaques, nodules, or cobblestone mucosa) were observed. Subsequently, the ultrasonic examination, transbronchial aspiration, and core biopsy were performed by a linear array ultrasonic bronchoscope (BF-UC-260F-OL8, Olympus, Tokyo, Japan) with a dedicated 22-gauge needle (NA-201SX-4022, Olympus). The systematical image of regional lymph node stations of the mediastinum and hilar regions were obtained and were measured (particularly the short axis diameter) using an international staging system[7]. Lymph nodes with a diameter $\geqslant$10 mm were selected based on real-time ultrasonic needle guidance. For each bronchoscopist, the number of passes was determined based on the amount of obtained biopsy material. To avoid contamination of the bronchial epithelium, an internal sheath was placed inside the needle during every puncture. After the needle was passaged into the targeted lymph node, the sheath was removed. Complications were carefully recorded.

### 2.3. Specimen preparation

Using air in the syringe, all TBNA specimens were aspirated from the needle onto a slide. Then with the help of another slide, the smear was performed and was immediately fixed in 95% alcohol. Ziehl-Neelsen staining was performed for each TBNA slide to detect mycobacteria. Routine stainings for morphologic evaluation were also performed and samples were sent for culturing of bacteria and fungi.

### 2.4. Final diagnosis

All aspirated specimens were categorized according to their pathological report. Specimen with frank malignant cells was considered as malignant, while specimen with obvious benign etiologies as benign. Inadequate samples were defined as samples only with blood, mucus, benign bronchial epithelial cells, or without lymphoid tissue. Other results of EBUS-TBNA were considered non-diagnostic. For these cases, mediastinoscopy or lymph node dissection was used to subsequently confirm the lymph nodes in surgical candidates. If benign lymphadenopathy was diagnosed by EBUS-TBNA, surgical staging of the mediastinum or clinical and radiological follow-up for at least six months would be performed subsequently.

Sarcoidosis was diagnosed according to the following criteria: (a) clinicoradiologic result in line with sarcoidosis; (b) demonstration of non-necrotizing granuloma; (c) no other known causes of granulomatous pulmonary diseases such as mycobacteria or fungal diseases; and (d) response to steroid therapy. They would be diagnosed as sarcoidosis if patients did not exhibit symptoms of granuloma, clinical stability or improvement, response to steroids therapy, or with no alternative diagnosis during six-month follow-up. Patients with granulomatous infammation with Langham's giant cells in histologic result or positive TB cultures were diagnosed as TB. After at least a six month follow-up, only two respiratory specialists reached consensus, the fnal diagnosis of active pulmonary TB was reconfrmed. If there was any ambiguities, another chest physician or radiologist could provide independent review to resolve. Considering the high prevalence of TB in China, patients with a positive acid fast bacilli smear in bronchoalveolar lavage fluid were also included.

### 2.5. Statistical analysis

Data were analyzed with Statistical Package for Social Sciences

(SPSS) version 20 software and wre expressed as percentages (for the categorical variables) or as the mean ± standard deviation (for the continuous variables). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) [including 95% confidence intervals (*CI*s)] were calculated with GraphPad InStat 3.05 software (GraphPad Software, San Diego, CA, USA). Categorical variables were compared with the *Chi*-square test. The *t*-test was applied to compare the continuous variables that exhibited a normal distribution, and the Mann-Whitney *U* test was applied for the continuous variables that did not exhibit a normal distribution. The difference was considered as different as $P$-value < 0.05.

## 3. Results

### 3.1. Clinicopathologic characteristics

The average age was 55 years (range, 44–62 years) and there were 148 (73.6%) male patients. The average size of mediastinal lymph node was 18 mm (range, 12–60 mm). The average number of needle passaging into a node was 2 (range, 1–6). The average duration of EBUS-TBNA was (25.8 ± 9.0) min. Samples from the paratracheal (groups 2 & 4) ($n$ = 106, 35.5%) and subcarinal (group 7) ($n$ = 68, 22.7%) lymph nodes accounted for more than half of samples (Table 1). No serious complication occurred.

**Table 1**
Characteristics of mediastinal lymphadenopathy cohort.

| Parameters | Benign disease | Malignancy | Total |
|---|---|---|---|
| No. of patients [*n* (%)] | 48 (23.9) | 153 (76.1) | 201 (100.0) |
| No. of males [*n* (%)] | 31 (15.4) | 117 (58.2) | 148 (73.6) |
| Mean age (years) (range) | 42 (22–51) | 57 (14–66) | 55 (44–62) |
| No. of sites sampled [*n* (%)] | 81 (27.1) | 218 (72.9) | 299 (100.0) |
| Node size (mm) (range) | 15 (5–25) | 21 (13–60) | 18 (12–60) |
| No. of passages (range) | 2 (1–6) | 2 (1–5) | 2 (1–6) |
| EBUS time (min) (mean± SD) | 24.0 ± 8.5 | 26.5 ± 9.2 | 25.8 ± 9.0 |
| Lymph nodes biopsied by EBUS-TBNA [*n* (%)] | | | |
| 2R | 5 (1.7) | 15 (5.0) | 20 (6.7) |
| 3 | 6 (2.0) | 16 (5.4) | 22 (7.4) |
| 4R | 18 (6.0) | 54 (18.1) | 72 (24.1) |
| 4L | 2 (0.7) | 12 (4.0) | 14 (4.7) |
| 7 | 25 (8.3) | 43 (14.4) | 68 (22.7) |
| 10R | 7 (2.3) | 9 (3.1) | 16 (5.4) |
| 10L | 2 (0.6) | 10 (3.3) | 12 (3.9) |
| 11R | 15 (5.0) | 46 (15.4) | 61 (20.4) |
| 11L | 1 (0.3%) | 10 (3.4%) | 11 (3.7%) |
| 12R | 0 (0.0%) | 3 (1.0%) | 3 (1.0%) |

Note: EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; R, right; L, left.

### 3.2. EBUS–TBNA diagnoses

Of the 201 patients, 153 (76.1%) received malignant final diagnosis, while 48 (23.9%) received a benign final diagnosis. A total of 108 (70.6%) patients in the malignancy group were diagnosed as non-small lung cancer. Other malignancies included small cell carcinoma ($n$ = 33), lymphoma ($n$ = 4), and metastatic cancers ($n$ = 8). A total of 29 patients were diagnosed as TB. The other benign diagnoses included sarcoidosis ($n$ = 7), reactive lymphadenopathy ($n$ = 7), esophageal cyst ($n$ = 2), and mediastinal abscess ($n$ = 3) (Table 2).

**Table 2**
Diagnosis yield of EBUS-TBNA.

| Final diagnoses | EBUS-TBNA diagnoses | *n* (%) |
|---|---|---|
| Benign disease ($n$ = 48) | | 48 (100.0) |
| Tuberculosis ($n$ = 29) | Necrotising granulomatous inflammation | 21 (43.7) |
| | Nonspecific inflammation | 6 (12.5) |
| | Inadequate specimen | 2 (4.2) |
| Sarcoidosis ($n$ = 7) | Non-necrotising granulomatous inflammation | 5 (10.4) |
| | Nonspecific inflammation | 2 (4.2) |
| Reactive lymphadenopathy | Inflammation | 7 (14.6) |
| Esophageal cyst | Esophageal cyst | 2 (4.2) |
| Mediastinal abscess | Mediastinal abscess | 3 (6.2) |
| Malignancy ($n$ = 153) | | 153 (100.0) |
| NSCLC ($n$ = 108) | NSCLC | 91 (59.5) |
| | Inflammation | 5 (3.3) |
| | Inadequate specimen | 11 (7.1) |
| | No sampling | 1 (0.7) |
| Small cell carcinoma | Small cell carcinoma | 33 (21.6) |
| Lymphoma ($n$ = 4) | Lymphoma | 1 (0.7) |
| | Inadequate specimen | 3 (2.0) |
| Metastatic cancer ($n$ = 8) | Metastatic cancer | 2 (1.3) |
| | Inadequate specimen | 6 (3.9) |

Note: EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; NSCLC: non-small cell lung cancer.

Nodal malignancies in 127/153 (83.0%) patients were successfully identified by EBUS-TBNA, and there were 26 false-negative cases. In one case, sampling was failed due to obscured target hilar lymph node by major blood vessels. In ten patients, EBUS-TBNA indicated inflammation, while progressive nodal enlargement on serial imaging, or significant fluorodeoxyglucose increase on positron emission tomography-CT indicated that thoracotomy was needed for final diagnosis. In another 15 patients, negative EBUS-TBNA result indicated high clinical suspicion of malignancy, then a thoracoscopy, biopsy of a different lymph node station, or a repeated EBUS-TBNA was performed to confirm. The repeat procedures were not included in our analysis.

Twenty-nine patients received final diagnosis of TB. Among these cases, 3 specimens exhibited positive smear in combination with necrotising granulomatous inflammation, and 18 specimens exhibited necrotising granulomatous inflammation. The high pre-test probability for TB infection showed that 8 patients (27.6% of all the patients with a final diagnosis of TB) had a diagnosis of TB following a non-diagnostic EBUS-TBNA. These patients underwent biopsies of other sites by an alternative procedure and necrotising granulomatous inflammation was observed.

Seven patients had final diagnosis of sarcoidosis. Among them. it was proven by histology or cytology diagnosis in 5 patients, while 2 patients exhibited rapid improvement after the administration of steroids. Seven patients received diagnosis of reactive lymphadenopathy based on a non-diagnostic EBUS-TBNA.

EBUS-TBNA showed sensitivity of 87.9% (124/141) (95% *CI*: 81%–92%), specificity of 100.0% (124/124) (95% *CI*: 74%–100%), PPV of 100.0% (124/124) (95% *CI*: 97%–100%),and NPV of 41.3% (95% *CI*: 23%–61%) for the detection of lung cancer. The sensitivity, specificity, PPV and NPV for diagnosis of mediastinal TB lymphadenitis were 72.4% (21/29) (95% *CI*: 53%–87%), 100.0% (95% *CI*: 82%–100%), 100.0% (95% *CI*: 84%–100%) and 70.3% (95% *CI*: 50%–86%). And sensitivity, specificity, PPV and NPV for sarcoidosis were 71.4% (5/7) (95% *CI*: 29%–96%), 100.0% (95% *CI*: 91–100%), 100.0% (95% *CI*: 48%–100%) and 95.3% (95% *CI*: 84%–99%).

## 4. Discussion

EBUS-TBNA is a new technology of bronchoscopy and is increasingly being used to diagnose unexplained mediastinal and hilar lymphadenopathy due to malignant or benign disease. The application of convex probe EBUS-TBNA in sampling mediastinal nodes was firstly reported by Krasnik *et al* in 2003[8]. Subsequently, rapid on-site cytological evaluations have enhanced the diagnostic yield of EBUS-TBNA[9]. Both left (L) and right (R) lymph node stations are accessible for EBUS-TBNA including 2R, 2L, 3, 4R, 4L, 7, 10R, 10L, 11R, 11L, and 12R[10]. Several studies have also demonstrated that EBUS-TBNA has equivalent diagnostic sensitivity to surgical mediastinoscopy[1,11]. For patients with potentially resectable non-small cell lung cancer with minor complications, EBUS-TBNA has replaced mediastinoscopy[1]. Furthermore, a systematic review of more than 1 600 patients underwent EBUS-TBNA showed that no significant complications associated with EBUS-TBNA occurred during diagnosis of mediastinal lymphadenopathy[12]. Our study further proves that EBUS-TBNA is effective and safe in the diagnosis of both benign and malignant lymphadenopathies.

This retrospective analysis demonstrated an excellent diagnostic performance of EBUS-TBNA in detecting nodule malignancy. The sensitivity and specificity were very high (87.9% and 100.0%, respectively) for the detection of lung cancer, and these percentages were similar to study of Herth *et al* (89.0% and 98.9%, respectively) [13]. However, the use of cytological needles for EBUS-TBNA compromises the maintenance of tissue architecture in the samples collected, and this decreases the diagnostic accuracy and subtyping of some metastatic cancers and mediastinal lymphomas. In the present study, EBUS-TBNA detected lymphoma in only one (25%) patient, and three patients required a surgical biopsy to confirm. Several authors[14,15] have criticized the use of EBUS-TBNA for some lymphoma subtypes, such as marginal zone lymphomas or hypocellular variants, due to the small volume of the samples. However, it is possible that the use of a 21G cytology needle with on-site cytopathological support and additional passes to collect an adequate sample could facilitate investigations of suspected lymphomas with EBUS-TBNA and may decrease the use of invasive procedures such as mediastinoscopy[16].

Few studies have investigated the capacity of EBUS-TBNA to diagnose benign disease, including sarcoidosis and TB. This study indicates that EBUS-TBNA provides high diagnostic sensitivity and specificity for TB lymphadenitis and sarcoidosis (72.4% *vs.* 71.4% and 100.0% *vs.* 10.00%, respectively). Furthermore, there was no significant difference in the sensitivity and specificity of EBUS-TBNA for a diagnosis of lung cancer versus TB or sarcodosis ($P$>0.05).

EBUS-TBNA has made it possible to obtain a diagnosis of sarcoidosis with a simple single day procedure rather than performing an invasive procedure such as rigid bronchoscopy, mediastinoscopy, or surgical lung biopsy[17]. Moreover, most published studies have reported that diagnostic yield of EBUS-TBNA was ~80% for detection of sarcoidosis[18-21]. In the present study, sarcoidosis was confirmed in 5 out of 7 patients (71.4%) by histology or cytology with EBUS-TBNA. Similarly, in a meta-analysis, which selected more than 550 patients with confirmed sarcoidosis predominantly at stage I and stage II[19], the overall diagnostic yield of EBUS-TBNA was 79% for detecting sarcoidosis. These results support the routine use of EBUS-TBNA to diagnose sarcoidosis.

EBUS-TBNA has become a ''standard of care'' to diagnose malignancy and sarcoidosis, yet it remains unclear whether this procedure can be used to assess enlarged thoracic nodes due to TB. The diagnosis yields of traditional techniques such as bronchoscopy and sputum cultures are low as treating patients with isolated mediastinal lymphadenopathy due to TB[22]. Mediastinoscopy is an alternative choice. However, general anesthesia should be required for mediastinoscopy, which may lead to a morbidity of 1%–2%. Besides, the posterior subcarinal and hilar nodes are inaccessible during the procedure[23,24]. Recently, EBUS-TBNA has been performed in detection of tuberculous mediastinal lymphadenopathy[24,25] and the diagnostic yield was ranged from 71%–89%. Similarly, our study displys a sensitivity of 72.4%. Thus, EBUS-TBNA is a satisfactory method to diagnose intra-thoracic TB. There are still some limitations in our study. First, rapid on-site cytological evaluations were not available due to cost and limited manpower. Rapid on-site cytopathological evaluation can provide optimal specimen preparation and assessment. In addition, it is helpful for further triage[26]. Beyond that, the resource of patients is limited. The finding of non-necrotising granulomatous inflammation in combination with supporting clinical evidence and response to therapy was considered to be consistent with a final diagnosis of sarcoidosis in the present study. It is possible that these observations would still be positive in patients with TB from a population with a high incidence of TB. Such patients may also clinically improve spontaneously and be classed inappropriately as responders to steroid treatment. Thus, additional prospective clinical research is needed for this population.

## Conflict of interest statement

The authors report no conflict of Interest.

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