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Miniforceps EBUS-guided lymph node biopsy: impact on diagnostic yield

Abstract

Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the standard diagnostic method for sampling mediastinal and hilar lymph nodes. Non-diagnostic samples have led some pulmonologists to add a miniforceps biopsy (EBUS-TBFB) in order to increase diagnostic yield. Our study aims to analyze the impact of adding EBUS-TBFB to the EBUS-TBNA in cases where Rapid On-site Evaluation (ROSE) was negative for malignancy or was non-diagnostic.

Material and methods: This retrospective chart review included 91 patients who were aged 18–90 years old and underwent EBUS with both TBNA and TBFB between January 1, 2013 and July 1, 2018.

Results: There was no significant statistical difference in the diagnostic yield of TBNA *vs* TBFB with a McNemar value of 0.167, and this conclusion was the same when stratified by race, age and lymph node size. Using TBNA as a gold standard, the sensitivity and specificity of TBFB was 87% and 69%, respectively. Out of the non-diagnostic TBNA samples on ROSE and cell-block, subsequent TBFB resulted in additional pathologic diagnoses in 16% of cases, of which 67% were non-caseating granulomas. Furthermore, two additional malignant cases were identified by TBFB consisting of small cell carcinoma and non-Hodgkin's lymphoma.

Conclusion: In conclusion, TBFB is a useful adjunctive tool in the diagnosis of non-malignant conditions (i.e. granulomatous diseases) with the potential to spare the patient from more invasive surgical biopsies. Training of future fellows in performing TBFB in addition to TBNA should be strongly encouraged.

Key words: EBUS-TBNA, EBUS-TBFB, sarcoidosis, Rapid On-site Evaluation, ROSE

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Introduction

Since its introduction in 1983 [1, 2], transbronchial needle aspiration (TBNA) has been a minimally invasive procedure for the sampling of mediastinal lymph nodes using bronchoscopy. However, the TBNA technique, in its infancy, was underutilized by clinicians because of its "blind" nature without direct real time visualization. In 2002, with the introduction of the convex probe endobronchial ultrasound (CP-EBUS), clinicians were finally able to perform real-time endobronchial visualization for TBNA. By 2007, EBUS-TBNA had become the routine method utilized by pulmonologists for the sampling of mediastinal and hilar lymph nodes [1–3].

The diagnostic yield of EBUS-TBNA varies greatly based on pathology. High yields have particularly been seen in the staging and diagnosis of non-small cell lung cancer (NSCLC) [1, 4–7].

Diagnostics yield for mediastinal lymphadenopathy in conditions such as lymphoma and granulomatous disease, however, remain under investigation. With regard to sarcoidosis, results are divided, with some reports of obtaining sufficient tissue for analysis, while others frequently resort to more invasive techniques such as mediastinoscopy for diagnosis [6, 8, 9]. The

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underlying reason for such variance in samples have been associated with the low tissue sample volume that is obtainable while using the standard 20–22–gauge needles for EBUS-TBNA.

The introduction of an additional biopsy using miniforceps (EBUS-TBFB) has been used to attempt to increase yield. Sample acquisition is performed through the initial hole made by the TBNA needle for obtaining diagnostic material from enlarged lymph nodes [6, 10–12]. Recent studies using TBFB for lymphadenopathy have shown improved yields; however, these studies have had their limitations that included lack of EBUS guidance, use of initial TBNA puncture site prior to performing TBFB, and/or Rapid On-site Evaluation (ROSE).

The use of the initial TBNA site as the entrance point for TBFB along with ROSE for both TBNA and TBFB sampling has been previously described to improve diagnostic yields with varying degrees of success. Our study aimed to analyze the impact of adding EBUS-TBFB to the EBUS-TBNA in cases where ROSE was deemed negative for malignancy or was non-diagnostic.

Material and methods

Data collection and patient inclusion

This study is a retrospective chart review of patients who underwent EBUS with both miniforceps biopsy and fine needle aspiration. Patients were eligible for analysis within age ranges of 18 to 90 years who had an EBUS procedure during the period from January 1, 2013 to July 2018. Data were collected only from those patients who underwent both EBUS-TBFB and EBUS-TBNA.

Exclusion criteria included any patient who had a diagnosis of cancer established with other testing modalities and any patient who did not have both EBUS with TBNA and miniforceps biopsy. Patients eligible for the chart review were identified from billing data. Data were collected by chart review from the electronic medical record eCare®.

Statistical analysis

Descriptive statistics were generated to characterize the study group. Categorical variables, such as sex, were described using frequency distributions. Continuous variables were described as the mean with standard deviation for normally distributed variables, and mode with an interquartile range for non-normally distributed variables. Sensitivity, specificity, positive predictive value, and negative predictive value were computed. Univariable analysis was done using the chi-squared test, Student's t-test, and analysis of variance. Multivariable regression was done using logistic regression. The diagnostic yields of EBUS-TBNA and a combined approach with EBUS-TBNA and EBUS-TBFB were compared with the McNemar test for dependent samples. $p < 0.05$ was considered statistically significant. All data were analyzed using SPSS v. 25.0, and a p-value of 0.05 or less indicated statistical significance.

This study was approved by the Ascension St. John Hospital Institutional Review Board.

Endobronchial ultrasound-guided transbronchial needle aspiration

A real-time EBUS scope (Model: Olympus BF-UC180F, Japan) was used in all cases. The EBUS scope uses a 6.9 mm outer diameter, a 2.0 mm working channel, and 30-degree oblique forward-viewing scope. A linear 7.5hz ultrasound transducer with 50 mm penetration capability was used for the visualization of each lymph node.

TBNA was performed using a 21-guage needle (Model: Olympus ViziShot EBUS-TBNA NA-201SX-4022, Japan). If visualization of adjacent vasculature was needed during TBNA, an integrated color Doppler US was utilized on a case-by-case basis under the discretion of the interventional pulmonologist. A minimum of 3 to 5 passes were performed at each station.

Endobronchial ultrasound-guided transbronchial forceps biopsy

For all TBFB biopsies, Boston Scientific "SpyBite biopsy" Forceps (Model: M00546270 USA) were used. After obtaining an EBUS-TBNA sample which was found to be non-diagnostic on initial ROSE, the sampled lymph node was evaluated by EBUS-TBFB. Our method of EBUS-TBFB for each sample was similar to that which had been previously described by Chrissian *et al.* [10]. While at the TBNA site, and after obtaining a sample via the jabbing technique, forceps were advanced to the orifice of the TBNA puncture site by direct visualization and confirmed via ultrasound (Figures 1, 2). When visualization of the puncture site was limited, an approximation of the initial angle of TBNA sampling was performed under ultrasound (Figure 2). Closed forceps were advanced into the lymph node through the initial puncture site at the same angle as our TBNA. The forceps were subsequently opened and advanced to obtain a sample against tissue resistance under continuous EBUS surveillance. Finally, the forceps were closed and withdrawn through the working

channel. In patients in whom TBNA or TBFB was unrevealing, the diagnosis was confirmed through surgical biopsy specimens of the mediastinum via mediastinoscopy, video-assisted thoracic surgery (VATS), or via a follow-up computerized tomography (CT) scan of the thorax.

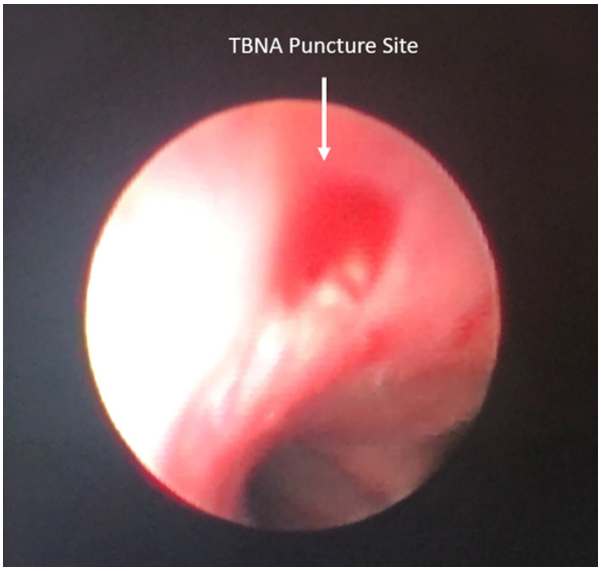

Figure 1. Direct visualization of the initial transbronchial needle aspiration puncture site prior to transbronchial forceps biopsy

Rapid on-site analysis

Fine needle aspiration samples obtained by TBNA were transferred onto glass slides, air dried, and subsequently mounted by the on-site pathologist. Rapid on-site cytology was performed and each of the three TBNA samples were processed individually by the on-site pathologist. TBFB samples were obtained only when TBNA samples were deemed non-diagnostic on initial ROSE. Tissue samples which were obtained from TBFB were placed in formalin immediately after acquisition. For TBNA samples, the Diff-Quick (Diff-Quik) Staining Protocol and light microscopy was performed by board certified on-site cytopathologists. Samples were subsequently sent for cell block analysis after ROSE was completed.

Post-operative monitoring

All patients were observed in the post-operative monitoring unit for 2 hours after the procedure. All patients with concerning post-procedur-

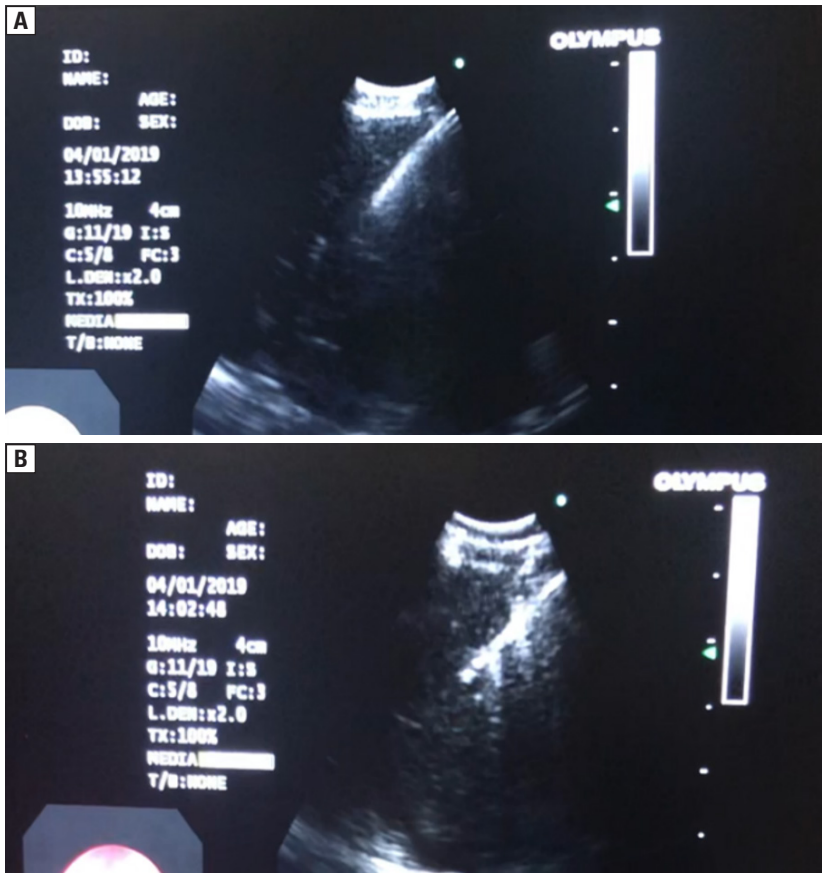

Figure 2. Correct angling of forceps within the lymph node. **A**. The original angle of transbronchial needle aspiration (TBNA); **B**. Angling of the transbronchial forceps biopsy to approximate the same approach as our initial TBNA with the forceps in an open position

al symptoms (i.e. chest pain, dyspnea, hemoptysis, or persistent tachycardia) underwent chest X-ray.

Results

The study group consisted of 91 patients who met the inclusion criteria. The mean age of patients in the study at the time of procedure was 57 ± 12.31 years old. 51.5% (47) were male and 58.2% were white (53). The mean BMI of patients was 28.2 ± 7.27. Subsequent lymph node biopsies were performed at stations shown in (Table 1) by the interventional pulmonologist with the most frequent locations being subcarinal (station 7), lower paratracheal (station 4), and interlobar (station 11). The mean lymph node size per CT imaging was 28.5 mm with a range from 6.0 to 90.0 mm.

ROSE was diagnostic of the final pathology in 39 cases (42.9%). There was no significant statistical difference in the diagnostic yield of TBNA *vs* TBFB with a McNemar value of 0.115. This conclusion was the same when stratified by age and size of lymph nodes with respective t-test values of 0.954, 0.651, and 0.139, as well as by gender and race with respective chi-square values of 0.923 and 0.280. Using TBNA as a gold standard, the sensitivity and specificity of TBFB was 87% (confidence interval of 73.74% to 95.06%) and 69% (confidence interval of 53.35% to 81.83%), respectively. Out of non-diagnostic TBNA samples on ROSE and cell-block, subsequent TBFB sampling resulted in additional pathologic diagnoses in 16% of cases, of which 67% were non-caseating granulomas. Furthermore, two additional malignant cases were identified via TBFB which were not diagnosed on TBNA. These consisted of small cell carcinoma and non-Hodgkin's lymphoma.

Table 1. Frequency of mediastinal and hilar lymph nodes examined by TBNA and TBFB

Station name	Station no	Frequency
Subcarinal	7	67
Lower paratracheal	4	60
Interlobar	11	44
Hilar	10	6
Lobar	12	4
Upper paratracheal	2	2

TBNA — transbronchial needle aspiration; TBFB — transbronchial forceps biopsy

Complications

No clinical complications were observed during EBUS-TBNA, EBUS-TBFB, or induction of anesthesia. All patients with concerning post-procedural symptoms (i.e. chest pain, dyspnea, hemoptysis, or persistent tachycardia) underwent chest X-ray without any complications being reported.

Discussion

In our study, we investigated the clinical utility provided by the addition of EBUS-TBFB

Table 2. Diagnostic yield of EBUS-TBNA, EBUS-TBFB, and ROSE

		EBUS-TBNA	EBUS-TBFB	Combined	ROSE
Overall diagnostic yield		54/91 (59.3%)	46/91 (50.5%)	60/91 (65.9%)	39/91 (42.9%)
Malignant		29			29
Small cell cancer		9/11	9/11		
NSCLC — total		20/20	11/20		
	Squamous cell cancer	5/5	4/5		
	Adenocarcinoma	14/14	6/14		
	Large cell carcinoma	1/1	1/1		
Benign					10
	Sarcoidosis	19/23	22/23		
Other*		6/6	6/6		
EBUS-TBFB *vs* EBUS-TBNA using the McNemar test					
Combined *vs* EBUS-TBNA using the McNemar test					

*Other: final diagnosis showing *Seminoma*, *Mycobacterium tuberculosis*, *Lymphangioma*, and bronchus-associated lymphoid tissue. EBUS-TBNA — endobronchial ultrasound-guided transbronchial needle aspiration; EBUS-TBFB — endobronchial ultrasound-guided transbronchial forceps biopsy; NSCLC — non-small-cell lung carcinoma; ROSE — Rapid On-site Evaluation

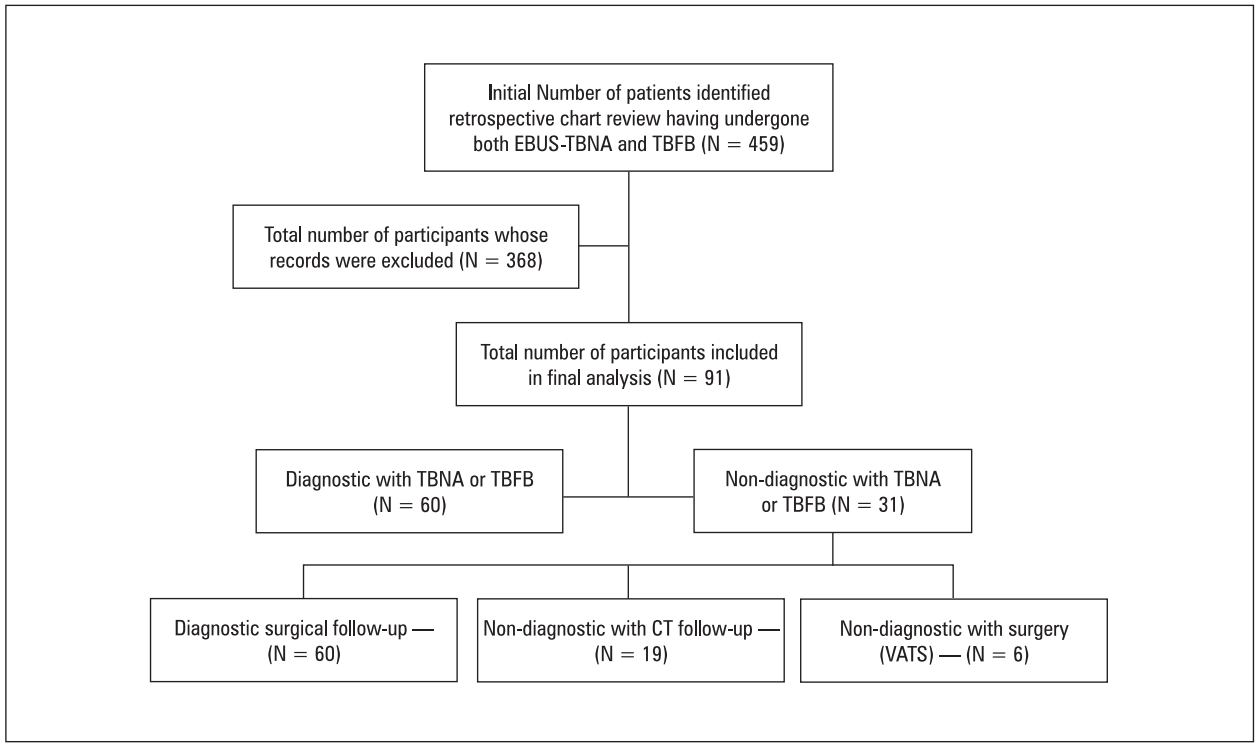

Figure 3. Flow chart illustrating the review, exclusion, and analysis of 459 patients who were initially selected, 91 of whom were eligible for analysis. VATS — video-assisted thoracic surgery; TBNA — transbronchial needle aspiration; TBFB — transbronchial forceps biopsy

to TBNA for obtaining the primary diagnosis and for sampling mediastinal and hilar lymph nodes. In the past, many patients underwent more invasive surgical biopsies via mediastinoscopy as the first line diagnostic modality. However, after the advent of EBUS-TBNA and many subsequent investigations of its utility, it has become the standard as a minimally invasive modality for evaluating concerning hilar and mediastinal lymph nodes. The sensitivity of EBUS-TBNA for diagnosing and staging NSCLC and SCC has been reported to be approximately between 84–94% [5, 6, 13–15]. In our study, the diagnostic yield achieved by EBUS-TBNA for NSCLC and SCLC were 100% (20/20) and 81% (9/11), respectively.

However, in granulomatous disease and lymphoma, EBUS-TBNA yield had been varied and, once again, many patients required the utilization of mediastinoscopy in order to obtain larger tissues samples than obtainable by TBNA [6, 8, 9]. Thus, in our study we have utilized EBUS-TBNA results on ROSE to examine the additive yield provided by the EBUS-TBFB especially in granulomatous diseases such as sarcoidosis. The diagnostic yield for Sarcoidosis within our study was 83% (19/23) which is higher than those reported in previous studies showing approximately 61% [16]. This, in turn, is likely multifactorial and can be affected by population prevalence, operator skill, and sample sizes obtained. Furthermore, the diagnostic yield of TBFB in our study was 96% (22/23), which is again higher than the previous value reported by Darwiche *et al.* [16] of approximately 89%. Finally, using TBNA as a gold standard, the sensitivity and specificity of EBUS-TBFB was 87% and 69%, respectively.

In this study, we have demonstrated that EBUS-TBFB appears to be safe. We had no significant bleeding, mediastinitis, pneumothorax, or intraprocedural death. Post-procedural chest X-rays were performed in patients with concerning symptoms (i.e. chest pain, dyspnea, hemoptysis, or persistent tachycardia) without any complications being reported.

In addition to its larger sample size and utilization of ROSE in each patient's sampling to ensure adequate sample volume acquisition, our study also utilized standard EBUS tools for both TBNA and TBFB. This allowed for easy replication and integration into current practice. This differs from previous studies which had utilized proprietary developed forceps with sharpened edges for easier penetration of the bronchial wall. Our study was also a single operator study as this procedure is very technique-dependent. As a result, the conclusions of this paper would

be stronger if it showcased results from multiple operators and multiple centers.

In conclusion, TBFB is a useful adjunctive tool in the diagnosis of non-malignant conditions such as granulomatous diseases with the potential to spare the patient from undergoing more invasive surgical biopsies. This approach is shown to be safe without increasing complication rates. Furthermore, in the current age of individualized targeted therapy for lung cancer, the additional tissue sample volume provided by TBFB may provide additional value to its incorporation into routine practice. Training of future fellows in performing TBFB in addition to TBNA should be strongly encouraged.

Conflict of interest

None declared.

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