



# Endobronchial ultrasound (EBUS)-guided transbronchial miniforceps biopsy an urban center experience

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**Background:** The role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in staging mediastinal and hilar lymph nodes in non-small cell lung cancer (NSCLC) is well established. However, evidence of its diagnostic utility in other pathologies—such as lymphoma—remains inadequate. This retrospective observational study aims to determine the diagnostic yield of EBUS-guided miniforceps biopsy (EBUS-MFB) compared to EBUS-TBNA in both malignant and nonmalignant conditions.

**Methods:** We conducted a retrospective cross-sectional chart review of all adult patients referred for EBUS at our institution between January 2019 and December 2022. All patients who underwent both EBUS-TBNA and EBUS-MFB were included, with some patients also undergoing transbronchial cryobiopsy. Patients without pathology reports available were excluded.

**Results:** The combination of EBUS-MFB and EBUS-TBNA had the highest percentage of diagnostic results both in the overall cohort (34.4%) and in patients who did not undergo transbronchial cryobiopsy (46.2%). EBUS-MFB alone yielded more diagnostic results compared to EBUS-TBNA. Transbronchial cryobiopsy was the sampling method with the highest percentage of diagnostic results in the cryobiopsy group (64.5%). Statistical analysis revealed a significant difference in diagnostic yield between EBUS-MFB and EBUS-TBNA ( $P < 0.001$ ), with EBUS-MFB showing a higher diagnostic yield overall. EBUS-MFB had a significantly higher diagnostic yield than EBUS-TBNA in benign cases, in patients diagnosed with sarcoidosis, but not in malignant disease.

**Conclusions:** Our study suggests that combining EBUS-MFB with EBUS-TBNA can improve the diagnostic yield, particularly in benign cases and sarcoidosis. These findings support the potential superiority of adding EBUS-MFB over EBUS-TBNA alone and highlight the need for further randomized control trials to validate these results. The retrospective nature of this study and certain limitations, such as the lack of adequate longer-term follow-up, selection and operator biases, and the absence of rapid on-site evaluation (ROSE) in some cases, should be considered when interpreting the results. Nonetheless, this study contributes to the growing evidence for the utility of EBUS-MFB in improving the diagnostic yield of EBUS procedures in specific clinical scenarios.

**Keywords:** Endobronchial ultrasound (EBUS); diagnostic yield; transbronchial needle aspiration (TBNA); miniforceps; cryobiopsy

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## Introduction

It has been two decades since the introduction of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Its role in staging the mediastinal and hilar lymph nodes in non-small cell lung cancer (NSCLC) is well established with sensitivity of 91% to 96%, even if lymph nodes are smaller than 1 cm (1,2). Conversely, the yield of EBUS-TBNA in other pathologies—like sarcoidosis and lymphoma—remains less than that of lung cancer in the case of sarcoidosis and inadequate in lymphoma (3). Of historical interest, Prakash *et al.* described a technique where he sampled subcarinal lymph nodes using flexible bronchoscopy forceps deployed through a track created by a 19-gauge needle (4). Oki *et al.* described a similar technique however they used fluoroscopic guidance (5). With the linear EBUS bronchoscope miniforceps biopsy (MFB) can be passed in real time into the mediastinal and hilar lymph nodes through a previously established tract after TBNA sampling. Shiari *et al.* showed that MFB to be useful adjunctive tool in the diagnosis of non-malignant conditions with the potential to spare patients more invasive surgical procedures (6). Our aim in this retrospective study was to determine the diagnostic yield of EBUS-guided MFB (EBUS-MFB) compared to EBUS-TBNA at our

institution in both malignant and nonmalignant conditions to examine if performing MFB after TBNA had any effect on the diagnostic yield. Patients that had EBUS-TBNA and EBUS-MFB who also had additional cryobiopsy in the same procedure were included. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-884/rc>).

## Methods

### Study design

We conducted a retrospective cross-sectional chart review at a tertiary referral center in Philadelphia, PA, USA. All adult patients referred for EBUS who underwent both EBUS-TBNA and EBUS-MFB between January 2019 and December 2022 were included. Patients were excluded if they did not have pathology results available. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Einstein Medical Center and Thomas Jefferson Hospital Institutional Review Board (IRB) (No. IRB-2023-1010). Informed consent was waived given the retrospective nature of the study.

### Procedure description

Two experienced interventional pulmonary physicians performed all the procedures in this retrospective analysis. EBUS scope (BF-UC180F; Olympus, Tokyo, Japan), Boston Scientific 1.2 mm CoreDx Miniforceps, and alternating 21- and 19-gauge Olympus fine needle aspiration (FNA) needles were used for EBUS, MFB, and FNA sequentially. All procedures were performed under general anesthesia with either a laryngeal mask airway or an endotracheal tube. In each case, the decision to perform EBUS-MFB was made by the interventional pulmonologist at their discretion during the procedure. Main reasons were to obtain enough specimens for accurate diagnosis and to provide more tissue for molecular analysis if malignancy was suspected. In cases where MFB was performed, the pulmonologist first obtained multiple samples (three samples at least if node 1 cm or larger) from the station using alternating 21- and 19-gauge Olympus FNA needles. Then using the tract created by the FNA needle the Boston Scientific CoreDx Miniforceps was passed into the lymph node under real time EBUS guidance. The number of MFBs performed at each

### Highlight box

#### Key findings

- Combining miniforceps biopsy (MFB) and transbronchial needle aspiration (TBNA) significantly improves diagnostic yield in mediastinal and hilar lymphadenopathy especially in nonmalignant conditions like sarcoidosis.

#### What is known and what is new?

- Prior research highlights the diagnostic benefits of MFB and TBNA when used together. Endobronchial ultrasound (EBUS) bronchoscopy is established as an effective tool for sarcoidosis, with a diagnostic yield of 87%.
- Our study adds to the body of evidence supporting combining MFB and TBNA in enhancing diagnostic outcomes.

#### What is the implication, and what should change now?

- The study suggests a shift toward using MFB with TBNA in EBUS bronchoscopy especially in benign diseases like sarcoidosis.
- Healthcare providers and guidelines committees should consider revising guidelines to reflect MFB's diagnostic benefits in certain clinical scenarios.
- Further research is essential to confirm and expand these findings, advancing EBUS bronchoscopy and patient care.

**Table 1** Indication for procedure

Indication	Number	%
Lung mass	51	41.8
Bilateral lymphadenopathy	32	26.2
Interstitial lung disease	17	13.9
Pulmonary nodule	17	13.9
Suspected infection	4	3.3
Cavitary lesion	1	0.8

**Table 2** Lymph node stations mean size

Site	Number	Mean $\pm$ standard deviation (mm)
Paratracheal	55	14.309 $\pm$ 9.334
Subcarinal	68	16.132 $\pm$ 10.285
Hilar	78	20.814 $\pm$ 21.569

station was based on the operator's discretion. Rapid on-site evaluation (ROSE) was not performed in all cases since it was introduced at our facility nearly halfway after the start date of this retrospective trial; logistical issues, variability of cytologist presence at the time of the procedures, and inadequate chart documentation regarding ROSE use prevented us from quantifying accurately the impact of this on diagnostic yield.

### Data collection

The following variables were collected from each patient's chart: age, sex, indication for procedure, TBNA biopsy site (paratracheal, subcarinal, and hilar), size of each lymph node biopsied, miniforceps lymph node biopsy site (paratracheal, subcarinal, and hilar), number of transbronchial cryobiopses performed (when applicable), final histopathological diagnosis, method(s) that led to final diagnosis and complications of the procedure.

If the procedure note did not indicate the size of the lymph node sampled, this information was obtained from the computed tomography (CT) or positron emission tomography (PET) scan resulting in the referral for EBUS. If there are multiple lymph nodes at the same station, then the largest lymph node is recorded. In cases where lymph node sizes were not documented and could not be obtained from CT or PET scans it was reported as not available (N/A).

### Definitions

A sample was defined as diagnostic if the result led to a definitive diagnosis without the need for further procedures. Indeterminate samples (i.e., if results did not yield a specific diagnosis or if the report showed only reactive inflammation and/or benign cells) were considered non-diagnostic. Diagnostic samples were then further categorized as malignant or benign. Diagnostic yield is calculated as the number of diagnostic samples divided by the total number of samples obtained. Diagnostic sample is considered one quantitatively per procedure if one, two, or three of the three lymph node stations were diagnostic and is considered as non-diagnostic if none of the stations yielded a clear diagnosis.

### Statistical analysis

Descriptive statistics were used to summarize the continuous variables, including age (years) and size of lymph nodes (mm). The mean, median, and standard deviation were calculated to describe the central tendency and dispersion of the data. To compare the continuous variables between the two groups, a *t*-test was used. To compare paired samples, MFB results (diagnostic *vs.* non-diagnostic) and TBNA results (diagnostic *vs.* non-diagnostic) McNemar test was used. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 29.0.0.0 software.

### Results

A total of 476 charts were reviewed, and 122 patients met inclusion criteria. The mean age was 63 years. In total, 45.9% were female, while the remaining 54.1% were male. *Table 1* shows the main indications for the procedure, with the most common indication being lung mass 41.8%, followed by bilateral lymphadenopathy 26.2%, interstitial lung disease and pulmonary nodule each in 13.9%.

*Table 2* outlines the mean and standard deviation of the lymph node size organized by site. Fifty-five samples were obtained from the paratracheal station with a mean size of 14.309 $\pm$ 9.334 mm, 68 samples from the subcarinal station with a mean size of 16.132 $\pm$ 10.285 mm, and 78 samples from hilar station with a mean size of 20.814 $\pm$ 21.569 mm. Mean size of lymph nodes was larger in the malignant group than in the benign group for all three regions, with mean sizes ranging from 12.85 to 18.63 mm for the benign group

**Table 3** Biopsy method yielding the final diagnosis

Method	Number	% <sup>†</sup>
MFB + TBNA combined	42	34.4
MFB alone	18	14.8
Cryobiopsy	14	11.5
TBNA	6	4.9
MFB + cryobiopsy	4	3.3
MFB + TBNA + cryobiopsy	2	1.6
Flowcytometry	1	0.8
Non-diagnostic	35	28.7

<sup>†</sup>, percentage of cases where method is diagnostic except in non-diagnostic category where the procedure was non-diagnostic overall. MFB, miniforceps biopsy; TBNA, transbronchial needle aspiration.

**Table 4** Biopsy method yielding the final diagnosis in patients who did not undergo cryobiopsy

Method	Number	% <sup>†</sup>
MFB + TBNA	42	46.2
MFB	15	16.5
TBNA	5	5.5
Flowcytometry	1	1.1
Non-diagnostic	28	30.8

<sup>†</sup>, percentage of cases where method is diagnostic except in non-diagnostic category where the procedure was non-diagnostic overall. MFB, miniforceps biopsy; TBNA, transbronchial needle aspiration.

**Table 5** Biopsy method yielding the final diagnosis in patients who had cryobiopsy

Method	Number	% <sup>†</sup>
Cryobiopsy	14	45.2
MFB + cryobiopsy	4	12.9
MFB	3	9.7
MFB + TBNA + cryobiopsy	2	6.5
TBNA	1	3.2
Non-diagnostic	7	22.6

<sup>†</sup>, percentage of cases where method is diagnostic except in non-diagnostic category where the procedure was non-diagnostic overall. MFB, miniforceps biopsy; TBNA, transbronchial needle aspiration.

and 17.46 to 18.45 mm for the malignant group. However, these differences were not statistically significant.

*Table 3* shows the biopsy methods used to determine the final diagnosis in all patients. The method that had the highest percentage of diagnostic specimens was the combination of MFB and TBNA, accounting for 34.4% of cases. MFB alone was the second most common method in 14.8% of cases. The table also highlights that only one patient was diagnosed using flowcytometry alone, and 28.7% of cases had non-diagnostic results.

*Table 4* displays the biopsy methods used to determine the final diagnosis in patients who did not undergo cryobiopsy. The biopsy method with the highest percentage of diagnostic specimens was combined MFB + TBNA, accounting for 46.2% of cases, followed by MFB alone in 16.5% of cases. Only 5 patients (5.5%) were diagnosed using TBNA alone, and 30.8% of samples obtained were non-diagnostic. *Table 5* illustrates the biopsy methods used to determine the final diagnosis in patients who underwent cryobiopsy. The biopsy method with the highest percentage of diagnostic specimens was cryobiopsy alone (45.2%), followed by a combination of MFB and cryobiopsy (12.9%), and a combination of MFB, TBNA, and cryobiopsy (6.5%). Only one patient was diagnosed using TBNA alone, and 22.6% of samples obtained were non-diagnostic.

*Table 6* displays the list of final histopathological diagnosis comparing MFB and TBNA diagnostic samples count in each diagnosis.

The only complication documented in the entire study population is pneumothorax which occurred in one patient.

#### **Comparison of diagnostic yield between MFB vs. TBNA**

Statistically significant difference was found when comparing the diagnostic yield of TBNA vs. MFB ( $P < 0.001$ ). The proportion of diagnostic samples obtained by TBNA was 38.5%, while the proportion of diagnostic samples obtained by MFB was 55.7%. These results suggest that MFB has a higher diagnostic yield than TBNA in the studied population.

After stratifying the diagnostic cases into benign or malignant a statistically significant difference in diagnostic yield between TBNA vs. MFB in benign cases favoring MFB ( $P < 0.001$ ), but not in malignant cases ( $P = 0.210$ ). The odds ratio (OR) for MFB in diagnosing benign cases was 2.071 [95% confidence interval (CI): 1.421–3.019], indicating a higher likelihood of diagnosis with MFB in

**Table 6** Final diagnosis histopathological

Final diagnosis by histopathology	MFB, n		TBNA, n	
	D	ND	D	ND
NSCLC	34	3	29	8
Small cell lung cancer	3	1	4	0
Adenocarcinoma of unknown primary	1	0	1	0
Metastatic breast cancer	1	0	0	1
Metastatic prostate cancer	2	0	2	0
Metastatic thyroid carcinoma	1	0	1	0
Low grade neuroendocrine tumor	1	0	0	1
Renal cell carcinoma	0	1	1	0
TB	0	1	0	1
NMTB	1	0	0	1
Sarcoidosis	13	5	5	13

MFB, miniforceps biopsy; n, number; TBNA, transbronchial needle aspiration; D, diagnostic; ND, non-diagnostic; NSCLC, non-small cell lung cancer; TB, tuberculosis; NMTB, non-mycobacterium TB.

benign cases compared to TBNA.

Finally, MFB had higher diagnostic yield in patients with sarcoidosis (n=18) compared to TBNA with (P<0.008).

## Discussion

Prior studies underscore the significant impact of EBUS-MFB in enhancing diagnostic yield across diverse clinical scenarios. When conventional TBNA alone reaches its limitations, the addition of MFB emerges as a transformative tool, facilitating substantial improvements in the diagnosis of conditions spanning granulomatous diseases, tuberculosis (TB), lymphoma, and NSCLC. An especially remarkable aspect is how MFB enhances diagnostic accuracy when ROSE yields negative results, sparing patients from the need for more invasive procedures (7-9). A 2008 prospective study by Herth *et al.* (3) used an approach similar to our facility with sequential 22/19-gauge needles then a MFB in 75 patients. A diagnosis was made in 36% of patients with the 22-gauge needle, 49% with the 19-gauge needle, and in 88% with the miniforceps. The increase in diagnostic yield with miniforceps was most significant in patients with sarcoidosis (88% *vs.* 36% for TBNA, P=0.001) or lymphoma (81% *vs.* 35%, P=0.038) (3). Another prospective study by Chrissian *et al.* in 2011 (10) included 50 patients undergoing EBUS-TBNA and EBUS-MFB. The overall diagnostic yield of EBUS-TBNA and EBUS-MFB was 81% and 91%,

respectively (P=0.09). The overall diagnostic yield increased to 97% (P<0.001) when the two techniques were combined. Additionally, a study conducted by Mehta *et al.* (9), has demonstrated that combining EBUS-TBNA and EBUS-MFB resulted in higher overall diagnostic yields, with an increase of up to 27%.

Incorporating our retrospective observational study results into the evidence, we observe an increase of the diagnostic yield of EBUS-MFB compared to EBUS-TBNA in both malignant and nonmalignant conditions. We found that the combination of EBUS-MFB and EBUS-TBNA yielded the highest percentage of diagnostic specimens in the overall cohort (34.4%) and in patients who did not undergo transbronchial cryobiopsy (46.2%). EBUS-MFB alone also yielded more diagnostic specimens compared to EBUS-TBNA, with statistical analysis revealing a significant difference in diagnostic yield between the two methods (P<0.001). Notably, EBUS-MFB showed a higher diagnostic yield overall and had a significantly higher yield in benign cases and patients diagnosed with sarcoidosis, although not in malignant disease. These findings support the potential superiority of adding EBUS-MFB over EBUS-TBNA alone, particularly in benign cases and specific clinical scenarios like sarcoidosis.

The American Thoracic Society (ATS) 2020 sarcoidosis guidelines report that EBUS has a diagnostic yield of 87%. However, it's essential to acknowledge the limitations and



gaps in current evidence and the heterogeneity of studies included in the analysis. Despite the advantages of EBUS in terms of invasiveness and costs, the guidelines note that the diagnostic yield of mediastinoscopy remains higher (98%), with approximately 13% of patients may still require mediastinoscopy, albeit at the cost of increased invasiveness, financial burden, and potential complications (11). Our study, although retrospective and limited in scope, contributes to this ongoing discussion by showcasing the potential of EBUS-MFB in improving diagnostic outcomes. While our findings support the superiority of adding EBUS-MFB over EBUS-TBNA alone, especially in sarcoidosis, further randomized controlled trials are warranted to provide more robust evidence and refine diagnostic algorithms especially if onsite ROSE is negative. In essence, our study aligns with the ATS guidelines and suggests that EBUS-MFB may be a valuable addition to the diagnostic armamentarium, potentially reducing the need for more invasive procedures and minimizing the associated risks and complications in select cases. Compared to prior randomized trials, we have a lower diagnostic yield for EBUS-TBNA (12,13). This can be explained by the lower rate of malignant samples (41%) and the high number of non-diagnostic specimens (27.9%). It is possible that some procedures were performed without high pretest probability for mediastinal disease, for example in cases when the indication for lymph node sampling was interstitial lung disease (13.9%).

The main limitations of our study were its retrospective nature and the liberal definition of diagnostic yield we used. An example of this methodological consideration can be seen in a study by Vachani *et al.* of peripheral nodules' diagnostic yield which demonstrated that different approaches in calculating the diagnostic yield results in estimates that can differ by more than 20% (14). Another potential limitation is the lack of longer-term follow-up in a sizable portion of the patients.

Furthermore, the introduction of ROSE cytopathological assessment halfway through the study period as prior literature has suggested that ROSE can be associated with higher diagnostic yield in EBUS-TBNA although this effect was not demonstrated in a 2018 meta-analysis performed by Sehgal *et al.* (7,15). The absence of ROSE earlier in the study period might have contributed to higher-than-average non-diagnostic samples and lower overall TBNA diagnostic yield. Unfortunately, our ability to precisely assess the impact of ROSE on diagnostic yield faced challenges due to logistical constraints, variations in cytologist availability

during procedures, and incomplete documentation of ROSE utilization in patient records. Moreover, the number of TBNA and MFB samples at each station exhibited non-standardized practices across patients. However, it is worth noting that, given our commitment to obtaining at least three samples from each station as per routine care, this variability may not have significantly influenced the overall diagnostic yield, as demonstrated in studies like Lee *et al.*'s where reported sample adequacy was 90.1% after the first pass, 98.1% after two passes, and reached 100% after three passes (16).

When analyzing the findings, it's crucial to recognize the potential for operator bias. This potential bias can also be compounded by selection bias, as patients who underwent EBUS who did not receive both MFB and TBNA were excluded. Additionally, it's worth noting that these procedures were exclusively performed by two highly experienced interventional pulmonologists at our facility, which could constrain the generalizability of our findings to less experienced bronchoscopists in other settings.

At the end while our study primarily focuses on the diagnostic yield of MFB in comparison to traditional TBNA, it's important to acknowledge the cost considerations associated with these procedures. The use of multiple tools, including a 21- and 18-gauge needle, in addition to miniforceps, does raise concerns about cost-effectiveness. However, it's worth noting that MFB, by potentially improving diagnostic accuracy, may prevent the need for more invasive and costly procedures like mediastinoscopy or potential expense of repeating the EBUS procedure in cases where the initial results are inconclusive. This possible cost-saving aspect should be factored into the overall cost-effectiveness analysis. Further research is needed to conduct a comprehensive cost-effectiveness analysis, taking into account factors such as equipment costs, procedural expenses, potential downstream cost savings resulting from accurate and timely diagnoses, and the cost of repeat procedures.

## Conclusions

In conclusion, our study suggests that combining MFB and TBNA can have higher diagnostic yield with statistically significant results, especially in nonmalignant conditions and in patients with sarcoidosis. This is in accordance with prior data suggesting that the addition of MFB is superior to TBNA alone in these specific cases. Furthermore, this study emphasizes the crucial need for further research to

substantiate these findings and calls for a reconsideration of the current EBUS guidelines. Specifically, we advocate for the inclusion of MFB in the diagnostic armamentarium, especially for sarcoidosis cases, potentially mitigating the necessity for more invasive and costly procedures like mediastinoscopy. This comprehensive approach not only reduces healthcare expenditure but also minimizes patient discomfort and associated risks, ultimately advancing the field of EBUS bronchoscopy and improving patient care.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-884/rc>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was reviewed and approved by the Einstein Medical Center and Thomas Jefferson Hospital IRB (No. IRB-2023-1010). Informed consent was waived given the retrospective nature of the study.

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