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Comparison of diagnostic yield and safety of endobronchial ultrasound-guided mediastinal lymph nodal cryobiopsy and endobronchial ultrasound-guided Franseen tip needle biopsy

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Abstract

In this prospective study, we evaluated the diagnostic yield and safety of two endobronchial ultrasound (EBUS) biopsy techniques – mediastinal cryobiopsy (EBUS-MCB) and Franseen tip needle biopsy (EBUS-ANB) – in patients with undiagnosed mediastinal lymphadenopathy. The study included 30 patients who underwent both EBUS-MCB and EBUS-ANB, with four biopsies taken from each patient using both methods. The results demonstrated that EBUS-MCB provided a higher diagnostic yield (96.4%) compared to EBUS-ANB (73.3%). Specimens from EBUS-MCB showed fewer artifacts and a higher density of granulomas and were adequate for ancillary studies in all cases. The most common complication observed was minor bleeding, which was more common with EBUS-MCB (36.6% *vs.* 13.3%, p=0.04). This study demonstrates that EBUS-guided cryobiopsy has a higher diagnostic yield when compared to EBUS-ANB and that both biopsy techniques have an acceptable safety profile. Larger studies comparing these two techniques are necessary to confirm the findings of the current study.

Key words: cryobiopsy, mediastinal lymph node, endobronchial ultrasound, Fransen tip needle, granuloma.

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Introduction

Endobronchial ultrasound (EBUS)-guided trans-bronchial needle aspiration (TBNA) is a minimally invasive endoscopic procedure for sampling mediastinal lesions. Since its introduction in the early 2000s, it has globally replaced mediastinoscopy and conventional TBNA as the initial diagnostic modality for any undiagnosed mediastinal lesion. The sample obtained by EBUS-TBNA from the nodes/masses is usually adequate to achieve a diagnosis, and meta-analyses have shown the overall diagnostic yield in lung cancer to vary between 88% and 93% [1-3]. However, for certain diseases such as lymphomas, benign granulomatous diseases, and rare tumors of the mediastinum, the diagnostic yield of EBUS-TBNA has been found to be lower and varies between 66% and 79% [1,4]. Hence, obtaining a histologic sample from the lymph nodes may be needed in such conditions. Also, with the recent advancements in lung cancer treatments, ancillary studies including immunohistochemistry and molecular markers have become essential, especially in non-small cell lung cancer. Procuring adequate and larger samples has now become a necessity [5].

Several techniques have been proposed to obtain a histologic sample/biopsy from lymph nodes *via* EBUS-TBNA. The three techniques of obtaining biopsy (EBUS-biopsy) are: i) EBUS-guided fine needle biopsy (EBUS-FNB) using needles such as the Olympus 19G TBNA needle, Cooks procore needle, or the Boston Franseen tipped Acquire biopsy needle [6]; ii) EBUS-guided intra nodal forceps biopsy (EBUS-IFB) [7]; and iii) EBUS-guided mediastinal Cryobiopsy (EBUS-MCB) [8]. The diagnostic yield of each of these EBUS-biopsy techniques has been shown to be superior to EBUS-TBNA in observational studies and randomized trials [9-12]. However, there are very few studies comparing the yield of different EBUS-biopsy techniques.

We have recently shown that the addition of EBUS-MCB to EBUS-TBNA in rapid on-site evaluation (ROSE) inconclusive cases increases the diagnostic yield by 43.7% [13]. A similar study was earlier published by Mehta *et al*. where they used the EBUS-IFB technique [14]. A recent randomized trial has shown EBUS-MCB to have a superior diagnostic yield when compared to EBUS-IFB [15]. Due to a lack of easy access to the dedicated EBUS biopsy forceps, EBUS-IFB is less often performed.

The advantages of EBUS-MCB include a higher diagnostic yield and the ability to obtain a larger and an artefact free sample. However, it has certain drawbacks. These include: i) the need for additional accessories (cryo machine, accessories for creating a tract into the nodes, and a cryoprobe); ii) the fact that the biopsies are usually obtained from a single node, and from one tract site within the node; and iii) the need to remove the scope en bloc with every biopsy pass. These disadvantages are overcome by using EBUS biopsy needles. When using the EBUS-FNB technique, multiple nodes can be biopsied, samples can be obtained from multiple areas within the node, and no additional accessories are needed.

There is no study comparing the performance of EBUS-FNB using acquire needles (EBUS-ANB) and cryobiopsy (EBUS-MCB) to date. In this study, we compare the procedural and diagnostic yield, safety, and sample adequacy between EBUS-MCB and EBUS-ANB.

Materials and Methods

This is a prospective study conducted between February 2023 and April 2023 at the Department of Pulmonary Medicine. During this period, all consecutive patients aged ≥18 years who underwent EBUS-TBNA for undiagnosed mediastinal lymphadenopathy (short axis size more than 1 cm on computed tomography (CT) of the chest) were included. Patients who underwent EBUS for mediastinal staging and those who did not consent to participate in the study were excluded. Ethics committee approval was obtained for the study (IRB No: RP/01/2023).

Endobronchial ultrasound biopsy procedure

All procedures were performed under general anesthesia using a laryngeal mask airway after obtaining written informed consent. All procedures were performed by two operators (VNM, VPP) with >10 years' experience in performing EBUS-TBNA. After the initial screening bronchoscopy, EBUS was performed using an Olympus BF-UC 180F EBUS bronchoscope (Olympus Medical Systems, Tokyo, Japan). A complete endo-sonographic assessment was made, and lymph node stations were identified, and the characteristics noted. The largest representative lymph node was chosen to be sampled.

Table 1. Clinico-demographic and mediastinal lymph-nodal characteristics of the study population (n=30).

Parameters	Values*
Age (years)	46.1±15.5
Sex	
Males	11 (36.6)
Females	19 (63.3)
Smoking status	
Never smokers	24 (80)
Reformed smokers	4 (13.3)
Current smokers	2 (6.6)
Lymph node station sampled by EBUS	
Station 4R	9 (30)
Station 7	15 (50)
Station 11L	3 (10)
Station 11R	3 (10)
Past history of malignancy/concurrent extra thoracic malignancy	8 (26.6)
EBUS node sono-characteristics	
Lymph node diameter (mm)	
Long axis	22.82±7.62
Short axis	18.40±7.39
Distinct margins	27(90)
Echogenicity of node	
Heterogeneous	16 (53.3)
Homogeneous	14 (46.6)
Shape	
Round	24 (80)
Oval	6 (20)
Central hilar structure present	3 (10)
Central intra-nodal vessel present	6 (20)

EBUS, endobronchial ultrasound. *Values expressed as n (%) or mean±standard deviation.

All patients underwent sequential 22-gauge Franseen tip needle (Acquire™ Pulmonary, Boston Scientific Corporation, Marlborough, MA, USA) biopsy (EBUS-ANB) and EBUS-MCB from the same lymph node. A Franseen tip needle biopsy was performed first. We performed passes till four core biopsies were obtained, and up to a maximum of eight passes. The samples obtained were fixed in formalin and sent for histopathological analysis. Following this, EBUS-MCB was performed. The 19-G Vizishot 2 flex TBNA needle (NA-U403SX-4019; Olympus Medical Systems, Tokyo, Japan) was used to create a tract into the lymph node through which a 1.1-mm cryoprobe (ERBE 20402-401; Erbe Elektromedizin GmbH, Tübingen, Germany) was introduced to obtain 4 biopsies. A maximum of 8 attempts was made, and the freezing time used was 5 seconds. The specimens were thawed in saline and then fixed in formalin. ROSE evaluation was not performed in this study.

The time taken for each procedure (in minutes), the number of passes attempted, the number of biopsies obtained, and intra-procedural and post-procedural complications (if any) were noted. Both biopsy specimens were sent separately for histopathological examination. The nodal biopsies obtained were assessed by a pathologist and were categorized as either a true biopsy (presence of lymphoid tissue) or a false biopsy (absence of lymphoid tissue with only blood clot or cartilage tissue). The histopathologic diagnosis and presence of hemorrhagic or edge crush artifacts were assessed by the pathologist. Procedural yield was defined as the percentage of all cases where lymph nodal tissue was identified on biopsy. Diagnostic yield was calculated only for the cases where a biopsy could be obtained. It was defined as the percentage of cases that had a definitive diagnosis on histopathologic examination. Patients who had only reactive lymph nodal tissue identified on the biopsy were followed up for 6 months, and a repeat CT chest was performed. If the nodes regressed or remained stable in size without an alternate diagnosis being established, they were classified as being true reactive lymph nodes.

The adequacy of the biopsy sample for further ancillary studies, like immunohistochemistry and molecular markers, was also analyzed by a pathologist. In patients in whom granulomatous inflammation was present on the biopsy, the number of granulomas visible per low-power field (LPF) was calculated, and the granuloma density was assessed. Presence of 1-5 granulomas per LPF was categorized as low granuloma density, 6-10 granulomas per LPF was categorized as intermediate granuloma density, and presence of >10 granulomas per LPF was categorized as a high granuloma density.

Data analysis

Data were analyzed using SPSS software (version 22.0). Data was presented descriptively. All continuous variables were described as mean±standard deviation, and all categorical variables were described in percentages. Comparison of variables was done by using chi square test/Fisher's exact for categorical variables, and the Mann-Whitney U test for the continuous variables. A p-value of <0.05 was considered as being significant.

Results

During the study period, a total of 42 patients underwent EBUS-TBNA, of which 30 patients fulfilled the inclusion criteria. (*Supplementary Figure 1*) All 30 patients underwent both EBUS-ANB and EBUS-MCB, sequentially (Figure 1). The demographic and lymph node characteristics of the study population are described in Table 1.

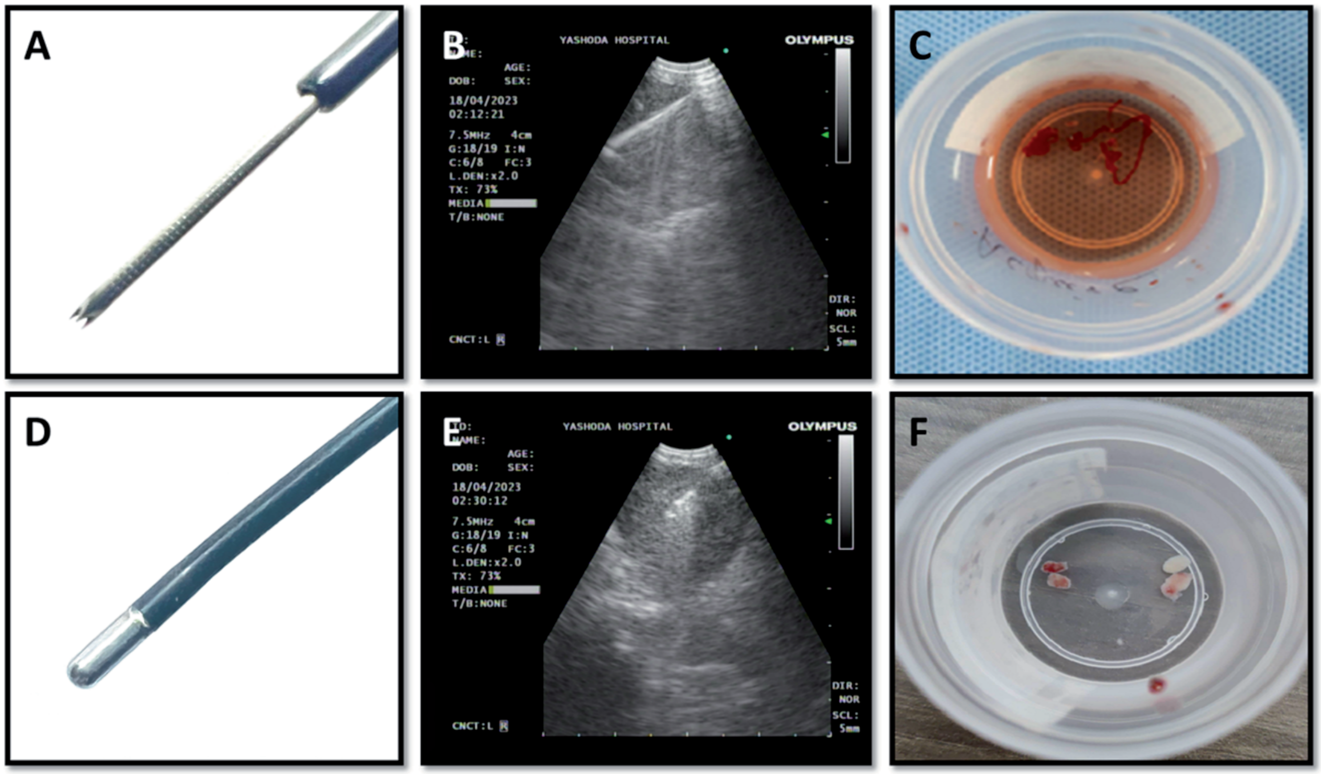

Figure 1. A) Image of Franseen Acquire biopsy needle showing the three pointed cutting edge; B) EBUS sonographic image with the Acquire biopsy needle within the lymph node; C) image showing linear cores obtained using Acquire biopsy needle; D) image of the 1.1 mm cryoprobe; E) EBUS sonographic image with the cryoprobe within the lymph node; F) image showing the nodal cryobiopsies obtained using the 1.1 mm cryoprobe.

Procedural and diagnostic yield

Of the 30 cases included, EBUS-MCB could not be performed in two cases because of the inability to create a tract large enough to obtain a biopsy using the 19-G needle. Of the 28 cases where a nodal cryobiopsy could be obtained, all had representative lymph node tissue in the biopsy specimen. Using the Franseen tip, core biopsies could be obtained in all cases. However, when analyzed by a pathologist, only 26 of the 30 cases had lymphoid tissue (true biopsies), and the remaining four were classified as false biopsies. The procedural yield of EBUS-MCB [28/30 (93.3%)] and EBUS-ANB [26/30 (86.7%)] was similar (p=0.67).

The most common histopathologic diagnosis (Table 2) in the study population was granulomatous inflammation (n=18), followed by malignancy (n=6) and reactive lymph nodes (n=5). Of the five cases where biopsy showed only reactive inflammation, one was later diagnosed to have disseminated tuberculosis (based on endometrial biopsy and broncho-alveolar lavage analysis). The remaining four cases were confirmed to have true reactive nodes after the 6-month follow-up. The diagnostic yield of EBUS-MCB was significantly higher when compared to the diagnostic yield of EBUS-ANB (96.4% *vs.* 73.3%; p=0.03).

Procedure time

The time taken to perform four cryobiopsies was significantly shorter when compared to the time taken to perform four needle biopsies [11.2 min *vs.* 13.2 min; p=0.01]. This is likely because of the additional time required to insert the stylet every time a needle biopsy needs to be performed. The number of passes/attempts needed to obtain four biopsies was similar in both arms (Table 3).

Biopsy quality and material adequacy

The biopsy obtained was assessed for the presence of any artefacts and for adequacy for ancillary studies by an experienced pathologist. The obtained biopsy was free of any pathologic artefacts in a higher percentage of cryobiopsies when compared with needle biopsies [15/28 (53.6%) *vs.* 4/30 (13.3%); p=0.001]. (*Supplementary Figure 2*) The mean size of the cryobiopsies obtained was 3.68±0.80 mm. Of the 6 cases where malignancy was confirmed, the EBUS-MCB sample was diagnostic and adequate in all, whereas the EBUS-ANB sample was non-diagnostic in one, and diagnostic but inadequate for further testing in one case. A higher density of granulomas was seen in the EBUS-MCB specimen as compared to EBUS-ANB specimens (Table 3, *Supplementary Figure 2*). The nature of granulomas was, however, similar in both biopsy specimens.

Adverse events

Both EBUS-ANB and EBUS-MCB were well tolerated by all the patients without any documented major adverse events. All the procedures were performed on an outpatient day care basis. The most common procedural complication noted in the study population was minor bleeding, which was more frequent with EBUS-MCB when compared with EBUS-ANB (36.65 *vs.* 13.3%, p=0.04). One case had a moderate bleed after EBUS-MCB, which required the instillation of local hemostatic agents and the application of fogarty occlusion balloon to control the bleed. No case of mediastinitis, pneumomediastinum, pneumothorax, or mediastinal fistula was encountered in the study population.

Discussion

To the best of our knowledge, this is the first study in the world literature that compared the diagnostic performance and safety of EBUS-MCB and EBUS-ANB. The results of the current study show that EBUS-MCB has a better diagnostic yield and procures larger and pathologic artefact-free biopsy samples when compared to EBUS-ANB.

EBUS-TBNA is the current investigation of choice for sampling mediastinal nodes. However, its limitations include a lower diagnostic yield in granulomatous diseases and lymphomas, and the inability to obtain sufficient tissue for ancillary studies. To overcome these limitations of EBUS-TBNA, several techniques to obtain a biopsy from mediastinal nodes *via* EBUS have been described and tested. These EBUS biopsy techniques include EBUS forceps biopsy, EBUS mediastinal cryobiopsy, and EBUS guided needle biopsy. Earlier studies have shown that all these biopsy modalities complement EBUS-TBNA and improve the diagnostic yield further [6,9,13]. To date, there are very few studies directly comparing the various EBUS biopsy techniques.

Though earlier studies have shown EBUS-IFB to increase the diagnostic yield over EBUS-TBNA [9,14], a recent randomized study that compared EBUS forceps biopsy to EBUS cryobiopsy has shown a higher diagnostic yield and a sample adequacy rate with EBUS cryobiopsy [15]. Further, dedicated forceps for performing EBUS-guided forceps biopsy are not commercially available in several countries.

Several dedicated histologic needles are now commercially available, and these include the ProCore™ needle (Cook Medical, Bloomington, IN, USA) [16,17], 19-gauge ViziShot™ Flex TBNA needle (Olympus Medical Systems, Tokyo, Japan) [18,19], and Franseen tip needles (Acquire™ Pulmonary, Boston Scientific Corporation, Marlborough, MA, USA) and SonoTip™ TopGain needle (Medi-Globe GmbH, Rohrdorf, Germany) [6,10]. Since their introduction for endoscopic ultrasound, Franseen tip needles have replaced other needles and are now the most often used needles for obtaining tissue biopsy via endoscopic ultrasound [20,21]. Hence, for the current study, we chose franseen tip *Acquire* needle Boston Scientific Corporation, Marlborough, MA, USA as our choice of histologic needle.

Table 2. Final histopathologic diagnosis of the study population* (n=30).

	EBUS-ANB (n=30), n (%)	EBUS-MCB (n=30), n (%)	Final histopathologic diagnosis
GI	14 (46.7)	18 (60)	18 (60)
Non necrotic GI	9 (30.0)	11 (36.7)	11 (36.7)
Necrotic GI	2 (6.7)	7 (23.3)	7 (23.3)
Ill-defined GI	3 (10.0)	0	0
Malignancy	5 (16.7)	6 (20)	6 (20)
Adenocarcinoma	3 (10.0)	4 (13.3)	4 (13.3)
Squamous cell carcinoma	1 (3.3)	1 (3.3)	1 (3.3)
Metastatic breast carcinoma	1 (3.3)	1 (3.3)	1 (3.3)
Reactive lymphoid tissue	7 (23.3)	3 (10)	5 (16.6)
Ectopic thyroid tissue	0 (0)	1 (3.3)	1 (3.3)
Lymph node tissue not obtained	4 (13.3)	2 (6.7)	-

EBUS-ANB, endobronchial ultrasound-guided acquire Franseen tip needle biopsy; EBUS-MCB, endobronchial ultrasound-guided mediastinal cryobiopsy; GI, granulomatous inflammation.

Table 3. Comparison of outcomes with endobronchial ultrasound (EBUS)-guided acquire Franseen tip needle biopsy and EBUS-guided mediastinal cryobiopsy.

Parameter	EBUS-ANB	EBUS-MCB	p
Number of passes performed	4.50±1.07	4.77±1.22	0.20
Number of biopsies obtained	3.93±0.36	3.73±1.01	0.53
Duration of procedure (min)	13.23±3.95	11.23±5.35	0.01
Procedural yield	26/30 (86.7)	28/30 (93.3)	0.67
Diagnostic yield	22/30 (73.3)	27/28 (96.4)	0.03
Granuloma density (n=18)			<0.01
Low	6/18 (33.3)	1/18 (5.6)	
Intermediate	6/18 (33.3)	1/18 (5.6)	
High	2/18 (11.1)	16/18 (88.9)	
Bleeding during procedure			0.04
Mild	4/30 (13.3)	11/30 (36.6)	
Moderate	0	1/30 (3.3)	
Hemorrhagic artifacts	8/30 (26.7)	4/28 (14.3)	0.34
Edge crush artifacts	25/30 (83.3)	10/28 (35.7)	<0.01

EBUS-ANB, endobronchial ultrasound-guided acquire Franseen tip needle biopsy; EBUS-MCB, endobronchial ultrasound-guided mediastinal cryobiopsy. Values expressed as n/N (%) or mean±standard deviation.

Several recent studies have assessed the diagnostic yield and performance of the newer EBUS-ANB, and the results of these studies are summarized in Table 4 [6,10,22-25]. In the current study, with EBUS-ANB, we obtained true cores in 86.7% (26/30) of cases. This rate of true core acquisition is similar to earlier published series where true cores were obtained in 72-87% of cases [6,10,22]. In up to 10-20% of cases, what visually appears as a tissue core, on microscopy, shows only blood clot or cartilage. This limitation can be overcome if imprint smears and ROSE are performed. Re-biopsy from a different area within the node can help procure true cores when ROSE does not show lymphoid aspirate. In the current study, ROSE was not performed.

The diagnostic yield with EBUS-ANB in the current study was 73.3% (22/30). This is comparable to the yield in earlier published series of Franseen tip needle biopsy, which varied from 60% to 97% [6,10]. In the current study, we sampled only the largest representative node with EBUS. This is unlike earlier published studies of the Franseen tip needle, where multiple nodes were sampled per patient. It is likely that if multiple identified nodes are sampled, the diagnostic yield of EBUS-ANB will be higher than that observed in this study.

EBUS-MCB is a novel technique for obtaining a biopsy from a lymph node. Since the first publication of EBUS-MCB by Zhang *et al*. [26], there is increasing interest on this technique because of the fact that the largest nodal biopsies are obtained by this technique [27]. The diagnostic yield of EBUS-MCB in earlier published studies ranged from 83-96% [28-30]. In two randomized controlled studies, the diagnostic yield of EBUS-MCB has been shown to be superior to EBUS-TBNA [8,31]. In the current study, the diagnostic yield of EBUS-MCB was 96.4%, which is similar to the yield observed in earlier published studies.

There is a lot of variability in the technique used for performing EBUS-MCB. The type of sedation/anesthesia used (moderate or deep sedation/general anesthesia), techniques used to create a nodal tract (needle *vs*. cautery knife), number of biopsies obtained (1-4 in number), and duration of activation of cryoprobe (3 to 7 seconds) are not yet standardized [32]. In the current study, we sampled only one node per patient, used 19G EBUS-TBNA needles to create a nodal tract, and performed four biopsies per patient using a 5-second freezing time. We could not obtain biopsies from two patients due to difficulty in creating a tract. This could have been overcome by utilizing a cautery knife for creating the tract. Of the 28 cases where a biopsy could be obtained, a confirmed diagnosis was achieved in 27 cases. One case was later confirmed to have disseminated tuberculosis.

In the current study, we have observed that the diagnostic yield of EBUS-MCB was superior to EBUS-ANB. The percentage of cases with no pathologic artefacts was significantly higher with EBUS-MCB, as there is no needle or forceps that cuts or crushes the tissue. Further, the pathologist's assessment of sample adequacy was higher in EBUS-MCB, both for benign and malignant diseases. The granuloma density was higher in biopsy specimens obtained by EBUS-MCB. This is likely due to the larger volume of tissue obtained and the lack of artefacts in a cryobiopsy sample. The sample adequacy of EBUS-MCB for ancillary studies in malignant cases was 100% with EBUS-MCB. This is similar to our earlier published study, where we have shown that all biopsies obtained with EBUS-MCB have sufficient material for performing all ancillary studies [13].

Most of the earlier published studies have shown a good safety profile with cryobiopsy and Franseen needle biopsy. In our study also, there were no major complications observed with EBUS-ANB, while one patient developed moderate bleeding with cryobiopsy, which was controlled with a fogarty balloon application. The comparison of the benefits and drawbacks of EBUS-MCB and EBUS-Franseen needle biopsy is summarized in *Supplementary Table 1*.

Our study has certain limitations. The sample size is small, and this is a single-center prospective study. The results of the study need to be replicated by other centers, and larger studies are needed before EBUS-MCB can be considered superior to the Franseen tip needle biopsy. The major pathology identified in our study was granulomatous inflammation, with only six cases diagnosed with malignancy. This was because we included all consecutive cases undergoing EBUS at our center. To determine and compare the biopsy sample adequacy for genetic testing and immunohistochemistry, studies with a higher proportion of malignant nodes need to be performed.

In this study, we compared only two techniques of performing mediastinal biopsy – cryobiopsy and Franssen tip needle biopsy.

Table 4. Summary of published case series and studies on endobronchial ultrasound-guided franseen tip needle biopsy.

Author (year)	Type of study	Needle type used	No of patients	True pathologic core biopsy acquisition rate	Diagnostic yield	Sample adequacy for ancillary studies
Balwan *et al.* (2020)	Retrospective cohort study	Boston Acquire 22G TBNA needle	100	87/100 (87%)	97/100 (97%)	NA
Oezkan *et al.* (2022)	Prospective observational study	Mediglobe Sonotip TopGain 22G needle	20	16/20 (80%)	12/20 (60%)	80%
Walscher *et al.* (2022)	Randomized controlled study	Mediglobe Sonotip TopGain 22G needle	15	21/46 (45.7%)	10/13 (77%)	NA
Brown *et al.* (2023)	Retrospective cohort study	Boston Acquire 22G TBNA needle	189	146/189 (77.2%)	174/189 (92.1%)	89-92%
Kramer *et al.* (2023)	Randomized controlled study	Boston Acquire 22G TBNA needle	76	54/72 (72%)	66/70 (94.3%)	92%
Aboudara *et al.* (2023)	Retrospective cohort study	Boston Acquire 22G TBNA needle	66	NA	60/66 (90.9%)	76%
Index study (2024)	Prospective study	Boston Acquire 22G needle	30	26/30 (86.7%)	22/30 (73.3%)	66.6%

NA, not available; TBNA, trans-bronchial needle aspiration.

Randomized studies comparing all three nodal biopsy modalities (forceps, cryo, and needle biopsy) need to be conducted. Further, there is also a need for well-designed studies comparing the yield of the various histologic needles that are now available.

Conclusions

EBUS-MCB has a higher diagnostic yield when compared to EBUS-ANB for diagnosing mediastinal lymphadenopathy. EBUS-MCB also provides a larger tissue, a pathologic artefact-free specimen, and a biopsy that is sufficient for ancillary molecular studies. Both EBUS-MCB and EBUS-ANB have an acceptable safety profile. Larger studies are needed to confirm the findings of this study.

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Online supplementary material:

Supplementary Figure 1. Flow of patients who underwent endobronchial ultrasonography during the study period.

Supplementary Figure 2. Photomicrographs comparing histopathologic images of Acquire needle biopsy (A, B, C) and Cryobiopsy (D, E, F). Image showing few granulomas with focal crush artefacts with Acquire needle biopsy (3A, H& E stain, magnification 40x), and an image with several well defined granulomas with necrosis and preserved nodal architecture with Cryobiopsy (3D, H& E stain, magnification 40x). Images of Acquire biopsy showing small cores (3B, H& E stain, magnification 10x) with few scattered and clustered adenocarcinoma cells admixed with small lymphocytes and fibrin (3C, H& E stain, magnification 40x). Images of Cryobiopsy showing multiple large fragments (3E, H& E stain, magnification 10x) with metastatic deposits of adenocarcinoma with surrounding desmoplasia and preserved lymph node architecture (3F, H& E stain, magnification 40x).

Supplementary Table 1. Advantages and disadvantages of endobronchial ultrasonography-guided Franseen tip needle biopsy and mediastinal cryobiopsy.

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