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Comparative yield of transbronchial cryo-nodal biopsy, transbronchial intra-nodal forceps biopsy, and transbronchial needle aspiration for mediastinal lesions at a tertiary care center in India (COLD-FORCEPS study)

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Abstract

Endobronchial ultrasound (EBUS)-guided mediastinal cryobiopsy and intranodal forceps biopsy are newer modalities for sampling mediastinal lymph nodes. The data regarding the diagnostic yield of both modalities is scarce. Patients were recruited retrospectively from our existing database. Patients who had undergone both an EBUS-guided mediastinal cryobiopsy and an intranodal forceps biopsy were enrolled in the study. The final diagnosis was made with a clinical-pathological-radiological assessment and clinical-radiological follow-up after 1 month. A total of 34 patients were enrolled in the study who had undergone both EBUS-guided mediastinal cryobiopsy and intranodal forceps biopsy and had complete data available, including 1-month follow-up data. The sample adequacy rate of EBUS-transbronchial needle aspiration (EBUS-TBNA), EBUS-TBNA with mediastinal cryobiopsy, and EBUS-TBNA with intranodal forceps biopsy was 94.11%, 97.05%, and 94.11%, respectively (p=0.56). The diagnostic yield achieved in EBUS-TBNA, EBUS-TBNA with mediastinal cryobiopsy, and EBUS-TBNA with intranodal forceps biopsy was 73.52%, 82.35%, and 79.41%, respectively (p=0.38). No major complications were seen in any patient. To conclude, adding EBUS-guided mediastinal cryobiopsy and intranodal forceps biopsy to EBUS-TBNA may not be superior to routine EBUS-TBNA.

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a technique for sampling mediastinal lymph nodes through the endobronchial approach. Historically, EBUS-TBNA can yield a diagnosis in only about three-fourths of patients [1]. There is abundant literature on techniques that can potentially increase the diagnostic yield of EBUS-TBNA, but despite innovations, refinements of techniques have not been uniformly accepted by pulmonologists worldwide.

Recently, there has been a growing interest in the use of cryotherapy for mediastinal lymph biopsy worldwide. Cryotherapy is a technique where a tissue is rapidly frozen using a cryoprobe and the removal of the cryoprobe leads to the extraction of the larger tissue, referred to as cryobiopsy [2]. Mediastinal

cryobiopsy involves using the principle of cryotherapy to sample tissue from mediastinal lesions. The cryoprobe is inserted through an endobronchial ultrasound (EBUS) bronchoscope and guided into the mediastinum under the guidance of ultrasound through the port created by EBUS-TBNA or using an electrocautery knife [3]. Literature on the utility of mediastinal cryobiopsy is still scarce. Existing literature suggests the addition of cryobiopsy to routine EBUS-TBNA can be helpful, but the lack of extensive research is reflected by the lack of standardization of the procedure.

Another technique that has received recent attention with respect to sampling of mediastinal lesions is intranodal forceps biopsy. In this technique, smaller-sized forceps are put through the port created, as required for cryobiopsy, under ultrasound guidance, and a biopsy sample is collected. There is a dearth of good quality studies for this procedure, but a recently published meta-analysis of existing studies has reported that the addition of intranodal forceps biopsy to EBUS-TBNA leads to a better yield but at the cost of higher adverse events [4]. To the best of our knowledge, we could not find a study showing the comparative efficacy of mediastinal cryobiopsy against intra-nodal forceps biopsy, and with this aim, we evaluated the data of procedures performed at our center.

Materials and Methods

The study was a retrospective observational study conducted in a large tertiary care and referral facility. Mediastinal cryobiopsies and intra-nodal forceps biopsies were performed following Indian EBUS guidelines and our hospital policy. The guidelines state that in case of a repeat procedure for a previous non-diagnostic EBUS-TBNA or in case of an inadequate pulmonologist rapid onsite evaluation (p-ROSE), a mediastinal cryobiopsy or a mediastinal forceps biopsy may be performed [5]. As per our hospital policy, in cases of repeat procedures for previous non-diagnostic EBUS-TBNA or in cases of inadequate p-ROSE, both mediastinal cryobiopsy and intranodal forceps biopsy are needed to be performed. We retrospectively extracted data from patients undergoing both mediastinal cryobiopsy and mediastinal forceps biopsy in the same sitting, from our existing database.

EBUS-TBNA was performed in the bronchoscopy suite using the BF-UC-180-F bronchoscope with EU-ME1 ultrasound processor systems (Olympus, Tokyo, Japan) and EB-530S bronchoscope with SU-1 processor systems (Fujifilm, Tokyo, Japan). All procedures were performed through the oral route under moderate, proceduralist-directed sedation. 10% lignocaine spray was applied to the pharynx. Topical anesthesia to the vocal cords and the tracheobronchial tree was achieved using cricothyroid injection of lignocaine solution. Both 21 Gauge (21G) and 19 Gauge (19G) needles were used (Olympus, Japan). Rapid on-site evaluation was performed for most procedures, by a pulmonologist (p-ROSE). Glass slide-fixed smears were prepared, and cell blocks were also processed. Aspirates were also processed for microbiological investigations, including AFB smear, Xpert Mtb-RIF test, and mycobacterial liquid cultures.

A transbronchial needle aspiration (TBNA) sample was considered adequate when it showed the presence of at least 40 lymphocytes per field on 40× magnification or if the slides were shown to be diagnostic for tuberculosis (TB), sarcoidosis, or malignancy. A diagnosis of TB was made if any microbiological investigation for TB was positive or if the cytopathological examination showed necrotizing granulomatous inflammation, with a compatible clinical-radiological profile. Sarcoidosis was diagnosed when the cytopathological analysis of the TBNA demonstrated non-necrotizing granulomas with consistent clinical-radiological profiles and no microbiological evidence of TB. A diagnosis of malignancy was considered when cytopathological analysis of TBNA showed tumor cells. As per our hospital protocol, all patients were followed up for 1 month for a clinical-radiological response after the procedure, and a final diagnosis was made after 1 month of follow-up.

All EBUS procedures were performed by experienced proceduralists. After the EBUS bronchoscope was introduced through the trachea, routine four EBUS-TBNA passes along with clot core samples were taken in all patients. p-ROSE was performed for all patients and in case of an inadequate p-ROSE, the patient was taken up for mediastinal cryobiopsy and intranodal forceps biopsy. After EBUS-TBNA, the site of EBUS-TBNA was localized, and an attempt to pass the 1.1 mm miniature flexible cryoprobe (ERBE, Medizintechnik, Tübingen, Germany) or 1.2 mm miniforceps through the port was made. In case of inability to penetrate the capsule of the lymph node with the cryoprobe or miniforceps, another port was created using a 19G/21G needle or using an electrocautery knife for 1-second actuation. After the port creation, cryoprobe and miniforceps were put through the port into the lymph node under ultrasound guidance. The freezing time used by all proceduralists for cryobiopsy was 5 seconds. By protocol, 2 samples of each cryobiopsy and forceps were taken before concluding the procedure in any order, chosen by the proceduralist.

Statistical analysis

The demographic details and procedural details were retrieved from the existing database, patient reports and procedural videos and entered in a Microsoft Excel file. Subjects with complete data on cytopathology and microbiological reports were included in the analysis. Statistical analyses were performed using the Stata 16 package (StataCorp LLC, College Station, TX, USA). Categorical variables were summarized as numbers (percentages), while quantitative variables as mean (standard deviation) or median (interquartile range). The Chi-squared test was used to compare categorical variables.

Results

Our facility acquired the 1.1 mm cryoprobe in July 2023. Since then, 132 EBUS-TBNA have been done in our department. Amongst these, p-ROSE was inadequate in 21 patients and these cases were taken up for mediastinal cryobiopsy or intranodal forceps biopsy. In addition, 35 patients were found to have a first-time non-diagnostic EBUS-TBNA and were planned for repeat EBUS with mediastinal cryobiopsy or intranodal forceps biopsy. Amongst 56 patients who underwent either cryobiopsy or intranodal forceps biopsy, we excluded the first 8 patients owing to the learning curve of the new procedures. We had data from 34 patients for final analysis who underwent both procedures and had complete data available including a 1-month follow-up. The consort diagram for the inclusion of patients is shown in Figure 1. The demographic data of enrolled patients is summarized in Table 1.

Our overall diagnostic adequacy and diagnostic yield for the EBUS-TBNA procedure were 97.05% and 82.35% respectively. The current study yield is summarized in Table 2. Based on histopathology, granulomatous etiology (n=18 patients) and malignant etiology (n=9 patients) were diagnosed in a total of 27 patients.

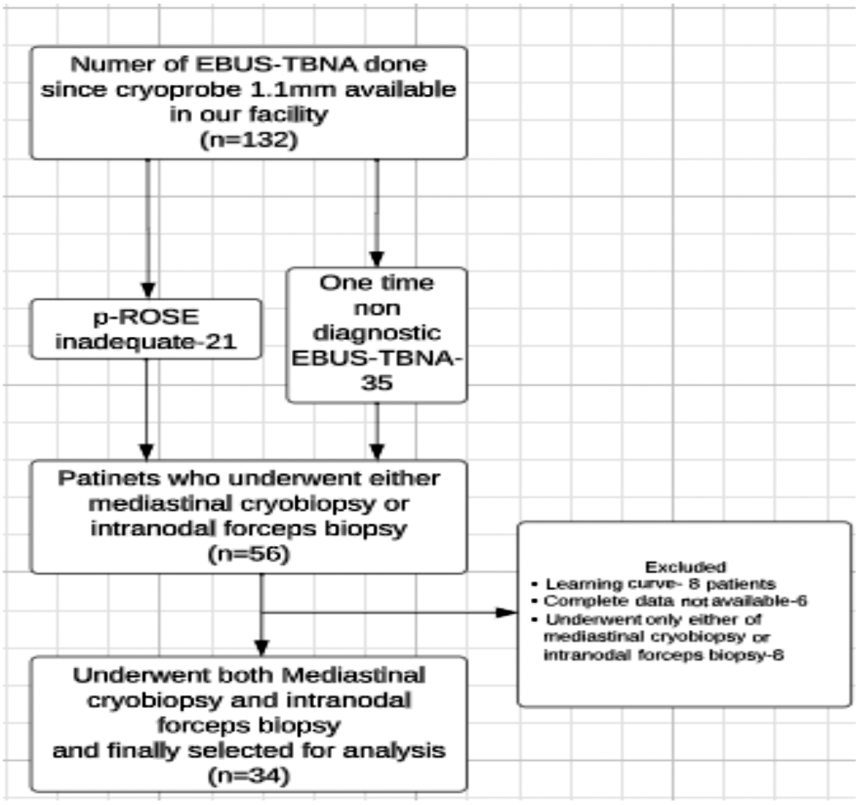

Figure 1. Consort diagram for selection of patients for analysis. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Table 1. Baseline characteristics of patients undergoing mediastinal cryobiopsy and intranodal forceps biopsy.

Characteristics	Patients (n=34)
Age (years), mean (±SD)	41.8 (±17.28)
Sex - male, n (%)	18 (52.9)
EBUS-TBNA, n (%): EUS-B-FNA, n (%)	33 (97):1 (3)
Clinical indication- number, n (%)	
Malignancy	15 (44.1)
Tuberculosis	9 (26.4)
Sarcoidosis	9 (26.4)
Lymphoma	1 (2.9)
Ultrasonographic characteristics, n (%)	
>1 cm	28 (82.3)
Shape - round	7 (20.5)
Distinct margins	21 (61.7)
Heterogenous	14 (41.1)
Coagulation necrosis present	6 (17.6)
Conglomeration present	12 (35.3)
Central hilar structure present	0
Calcification present	3 (8.8)

SD, standard deviation; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-B-FNA, transesophageal bronchoscopic ultrasound-guided fine needle aspiration.

Table 2. Diagnostic yield data of the various endobronchial ultrasound modalities for mediastinal lesions.

Yield data	EBUS-TBNA (%)	EBUS-TBNA with mediastinal cryobiopsy (%)	EBUS-TBNA with intranodal forceps biopsy (%)	p
Adequacy	94.11	97.05	94.11	0.56
Diagnosis yield	73.52	82.35	79.41	0.38

EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Based on clinical, radiological, and histopathological assessment, the most common diagnosis achieved was sarcoidosis (n=11), adenocarcinoma (n=4 patients), squamous cell carcinoma (n=1 patient), adenoid cystic carcinoma (n=1 patient), lymphoma (n=1 patient), undifferentiated malignancy (n=2 patients) and TB (n=7 patients). The mean lymph node size sampled was 14.08 (±3.91) mm. The number of passes taken for EBUS-TBNA was 4 for all patients. The number of cryobiopsy samples and intranodal forceps biopsy samples was 2 each for all patients. The median size (range) of the clot core sample, cryobiopsy sample, and intranodal forceps biopsy was 26 mm^3 (1-250), 16 mm^3 (1-180), and 1 mm^3 (1-60), respectively. Cryobiopsy and intranodal forceps biopsy were done from the same port as EBUS-TBNA in 27 (79.4%) patients, new port creation was required in 7 (20.5%), while new port using an electrocautery knife was done in 3 (8.8%) patients. The average procedure time including patient preparation and observation was 50.6 minutes. The most common lymph node sampled was subcarinal in 27 (79.4%) patients, while station 4L, 4R and 11R lymph nodes were sampled once each (2.9% each), and mediastinal masses were sampled 4 times. There were no major complications observed in any patient.

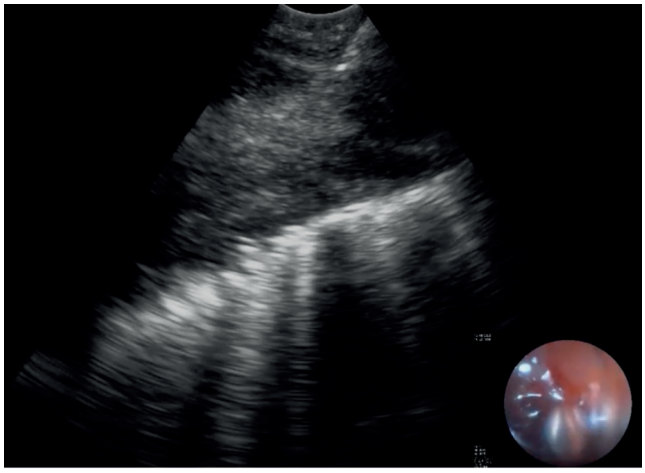

Figure 2. Transbronchial needle aspiration in the mediastinal lymph node through endobronchial ultrasound bronchoscope.

Discussion

EBUS-guided mediastinal cryobiopsy and intra-nodal forceps biopsy are new methods (Figures 2-4) in the field of pulmonary medicine. Researchers and interventional pulmonologists have keen interests in these two methods, often invoking strong responses when debating the additional role of these two modalities in mediastinal lymph node sampling. There is growing evidence in support of the two modalities, but most of the literature is confined to case reports and case series, and a few randomized trials (PubMed search) [3,6,7].

In the recent randomized controlled trial (RCT) of 197 patients, Zhang *et al*. compared EBUS-TBNA with cryobiopsy and found cryobiopsy to be superior (79.9% *vs*. 91.8%, p=0.001) [3]. The yield was not significantly different when malignant lesions were sampled and the difference was only seen when benign and uncommon tumors were sampled. They did not find any difference between when TBNA was done before cryobiopsy, in comparison to when cryobiopsy was done upfront. They used a criterion of size of more than 1 cm (short axis) for enrolment. The port was created using a high-frequency needle knife. All patients were treated under conscious sedation. In comparison, another study by Fan *et al*. enrolled 271 patients, using similar enrolment criteria of size more than 1 cm [7]. They compared EBUS-TBNA alone with EBUS-TBNA combined with cryobiopsy and found adding cryobiopsy to EBUS-TBNA as beneficial (81% *vs*. 93% respectively, p=0.0039). They also found the utility of cryobiopsy in benign disorders like the previous study. There were no major complications reported in either study.

Concerning EBUS-intranodal forceps biopsy, we could not find any RCT on the subject, though a recently concluded meta-analysis by Agrawal *et al*. of observational studies found that adding intranodal forceps biopsy to EBUS-TBNA was superior to EBUS-TBNA alone (67% *vs*. 92%, p<0.00001) [4]. The meta-analysis also found that with an increase in yield, there was an associated increase in complications. The rate of pneumothorax, pneumomediastinum, and bleeding were higher in the intranodal forceps biopsy group. To date, we do not have a study comparing the two novel methods.

In our study, all patients underwent both procedures subse-

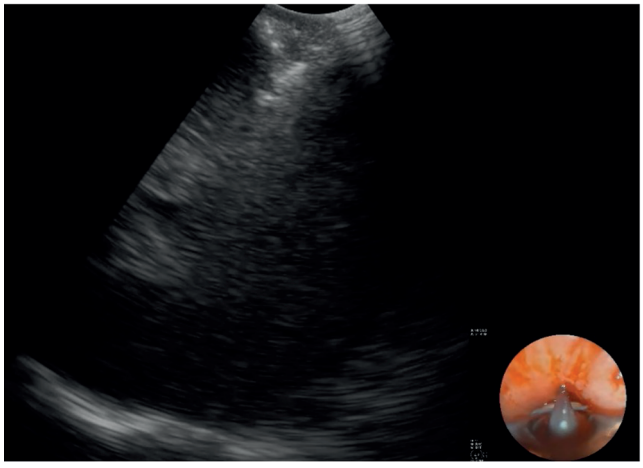

Figure 3. Cryoprobe *in situ* in the mediastinal lymph node through the Endobronchial ultrasound.

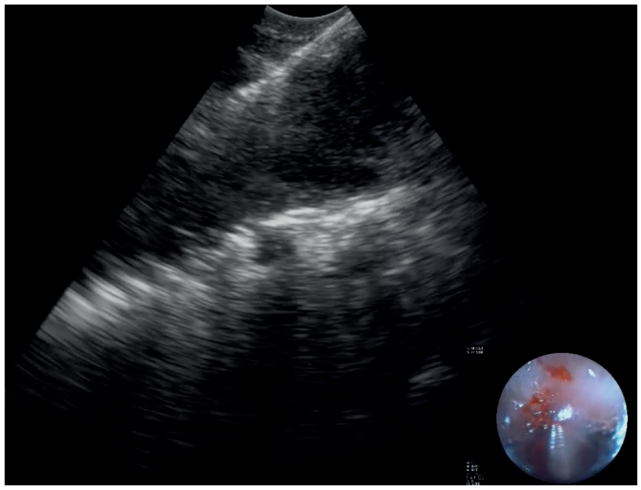

Figure 4. Intranodal biopsy forceps in situ in the mediastinal lymph node through the endobronchial ultrasound.

quently to routine EBUS-TBNA under conscious sedation. We did not find any significant advantage of adding cryobiopsy or intranodal forceps biopsy to routine EBUS-TBNA in our study. A possible reason could be that our study is real-world data and we have included patients with smaller lymph nodes also (<1 cm in short axis). 17.7% of our patients had lymph nodes less than 1 cm, and even though in these patients, the samplings were adequate, the diagnosis was not established, and there is a strong possibility that these lymph nodes might truly be reactive. Probably this is the reason why even though our EBUS-TBNA yield is in line with worldwide data, our biopsy data does not match the global results. Another possible explanation for relatively poorer results in comparison to worldwide data on intranodal forceps biopsy is not using CoreDX forceps (BOSTON Scientific, Boston, MA, USA) as used in other studies [8]. An important advantage we found of cryobiopsy is that it gives a larger viable tissue, and the need for repeat sampling for molecular and immunologic profiling in cases of malignancy is reduced. This may be a group of patients in whom mediastinal cryobiopsy and intranodal forceps biopsy may be useful upfront. Another caveat of mediastinal cryobiopsy is that, as fanning is not possible during the procedure, one ends up taking a sample from the same site of the same lymph node, as creating multiple ports is not a feasible option.

Another aspect of mediastinal cryobiopsy is that, in our experience, our first 8 patients (not included in the analysis) had an adequacy rate of 50% in mediastinal cryobiopsy, while subsequently, our adequacy rate has been 97.05%, thereby reflecting that it has a short learning curve for an EBUS trained personnel.

Although theoretically, potential major complications of the two procedures include pneumothorax, pneumomediastinum, life-threatening bleeding, and mediastinal infection, there were no major complications noted in our patients. Though we found both the procedures to be safe, it would certainly add to the cost and duration of the procedure, if done routinely, and may not be a magic bullet as endorsed by many. The procedure should be done in carefully selected patients, as a salvage procedure, or in patients who may require a larger tissue for molecular profiling like malignancy or lymphoma.

The strength of our study is that, despite its retrospective nature, all patients and lymph nodes sampled were common in the three arms, thereby eliminating enrolment bias, which is one of the major limitations of other observational studies. Another strength of our study is that national guidelines and our hospital policy were followed ensuring a standardized approach with respect to indication and procedure for all the patients. Thirdly, this is to the best of our knowledge, the first study comparing EBUS-guided mediastinal cryobiopsy and intra-nodal forceps biopsy. There are a few limitations to our study also. Our study had a small sample size, affecting the power of the study and making results not generalizable. In addition, pathologists were not blinded to the procedure done. Thirdly, since we were studying the additional advantage of adding mediastinal cryobiopsy or intranodal forceps biopsy to EBUS-TBNA, our population included only a sub-population where EBUS-TBNA was inconclusive, thus results may not be generalizable. Fourthly, since the order of techniques to be performed was not randomized, there could be a theoretical possibility of first pass bias, in which first pass technique could induce local hematoma and may reduce the yield of further techniques performed, and since the technique of cryobiopsy or intranodal forceps biopsy requires port creation using a knife or EBUS-TBNA needle, possibility of creating local hematoma cannot be circumvented. Lastly, sampling smaller-sized lymph nodes (<1cm) may have affected the diagnostic yield of the procedure.

Conclusions

EBUS-guided mediastinal cryobiopsy and intra-nodal forceps biopsy may not be superior to an adequately performed EBUS-TBNA and should not be done routinely as an upfront procedure. These newer techniques require more studies to evaluate their role in the evaluation of mediastinal lymph nodes.

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