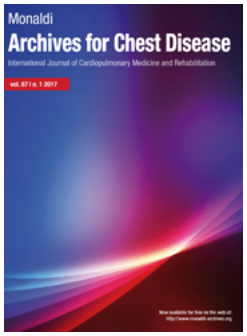

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Madan M, Mahendran AJ, Kumar R, et al. **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).** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2813

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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Contributions: MM, AJM, RK, YK, RK, PI, NKG, SC, NG, were involved in literature search, planning, conduct, writing the original draft of manuscript, literature search, and editing of the study; NG, is corresponding author and guarantor for all. All the authors have agreed with the submitted manuscript.

Conflict of interest: The authors declare that they have no conflicts of interest regarding current study.

Ethics approval and consent to participate: an ethical clearance was obtained from the institutional ethics committee of VMMC and Safdarjung Hospital, New Delhi vide serial number- S. No. IEC/VMMC/SJH/Thesis/9/2022/CC-14 dated 6.10.2022

Patient consent for publication: written informed consent has been taken from all patients for participation in the study, endobronchial procedure as well as for publication of the data.

Funding: the current study is not funded by any source.

Availability of data and materials: the clinical data and the study materials available from the corresponding author on reasonable request.

Acknowledgments: pulmonary residents and bronchoscopy room staff of the Department of Pulmonary Critical Care and Sleep Medicine, VMMC & Safdarjung Hospital, New Delhi-110029, India.

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 clinico-radiological follow-up after one 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.

Key words: lymph nodes, mediastinum; endoscopic ultrasound-guided fine needle aspiration/methods, ultrasonography, interventional.

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a technique of 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 removal of cryoprobe leads to 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 bronchoscope and guided into the mediastinum under the guidance of ultrasound through the port created by endobronchial ultrasound guided-transbronchial needle aspiration (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 standardisation of the procedure.

Another technique that has received recent attention with respect to sampling of mediastinal lesions is intranodal forceps biopsy. In this technique, a smaller-sized forceps is put through the port created, as required for cryobiopsy, under ultrasound guidance and 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 intra-nodal 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 centre.

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 in accordance with 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 of 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; Japan) and EB-530S bronchoscope with SU-1 processor systems (Fujifilm, Japan). All procedures were performed through the oral route under moderate, proceduralist-directed sedation. 10% Lignocaine spray was applied to the pharynx. Topical anaesthesia to the vocal cords and the tracheobronchial tree was achieved using cricothyroid injection of lignocaine solution. Both 21 Gauge and 19 Gauge needles were used (Olympus, Japan). Rapid On-site evaluation (ROSE) 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 40x magnification or if the slides were shown to be diagnostic for tuberculosis, sarcoidosis, or malignancy. A diagnosis of tuberculosis was made if any microbiological investigation for TB was positive or if the cytopathological examination showed necrotizing granulomatous inflammation, with a compatible clinico-radiological profile. Sarcoidosis was diagnosed when the cytopathological analysis of the TBNA demonstrated non-necrotizing granulomas with consistent clinico-radiological profiles and no microbiological evidence of tuberculosis. 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 clinico-radiological response after the procedure and final diagnosis was made after one month of follow up.

All EBUS procedures were performed by experienced proceduralists. After 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 localised, and an attempt to pass the 1.1mm 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. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Categorical variables were summarised as numbers (percentages), while quantitative variables as mean (SD) or median (IQR). The Chi-squared test was used to compare categorical variables.

Results

Our facility acquired the 1.1mm 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 of cryobiopsy or intranodal forceps biopsy, we had excluded the first 8 patients owing to the learning curve of the new procedures. We had data of 34 patients for final analysis who underwent both the procedures and had complete data available including a 1 month follow up. Consort diagram for inclusion of patients is shown in Figure 1. The demographic data of enrolled patients is summarised in Table 1.

Our overall diagnostic adequacy and diagnostic yield for EBUS-TBNA procedure has been 97.05% and 82.35% respectively. The current study yield is summarised in Table 2. On the basis of histopathology, granulomatous etiology (n=18 patients) and malignant etiology (n=9 patients) was diagnosed in a total of 27 patients. 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 tuberculosis (n-=7 patients). The mean lymph node size sampled was 14.08 (±3.91) mm. Number of passes taken for EBUS-TBNA has been four passes for all patients. Number of

cryobiopsy samples and intranodal forceps biopsy samples has been two each for all patients. Median size (range) of clot core sample, cryobiopsy sample and intranodal forceps biopsy were 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%) patients while new port using electrocautery knife was done in 3(8.8%) patients.

Average procedure time including patient preparation and observation was 50.6 minutes. 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 four times. There were no major complications observed in any patient.

Discussion

Endobronchial ultrasound (EBUS) guided mediastinal cryobiopsy and intra-nodal forceps biopsy are new methods (Figure 2-4) in the field of pulmonary medicine. Researchers and interventional pulmonologists are having 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 randomised trials (PubMed search) [3,6,7].

In the recent RCT by Zhang et al. of 197 patients, comparing EBUS-TBNA with cryobiopsy and found cryobiopsy to be superior (79.9% vs 91.8%, p=0.001) [3]. Yield was not significantly different when malignant lesions were sampled rather the difference was only seen when benign and uncommon tumours were sampled. They did not find any difference between when TBNA was done prior to cryobiopsy, in comparison to when cryobiopsy was done upfront. They used a criterion of size of more than 1 cm (short axis) for enrolment. Port was created using a high frequency needle knife. All patients were done under conscious sedation.

In comparison, the other 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.

With respect to 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 increase in yield, there was associated increase in complications also. Rate of pneumothorax, pneumomediastinum and bleeding were higher in the intranodal forceps biopsy group. Until date, we do not have a study comparing the two novel methods.

In our study, all patients underwent both procedures subsequently 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.possible reason could be that our study is real world data, we have included patients with smaller lymph nodes also (<1cm 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, but diagnosis was not established, and there is a strong possibility that these lymph nodes might truly be reactive lymph nodes. Probably this is the reason that even though our EBUS-TBNA yield is in line with worldwide data, our biopsy data is not matching the global results. Another possible explanation of relatively poorer results in comparison to worldwide data on intranodal forceps biopsy, is not using CoreDX forceps (BOSTON Scientific) as used in other studies [8]. An important advantage we found of cryobiopsy is that they give a larger viable tissue, and 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 which may require a larger tissue for molecular profiling like malignancy or lymphoma.

Strength of our study being, though a retrospective study, 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 standardised 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 were few limitations to our study also, our study had a small sample size, affecting the power of the study and results may not be 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 evaluation of mediastinal lymph nodes.

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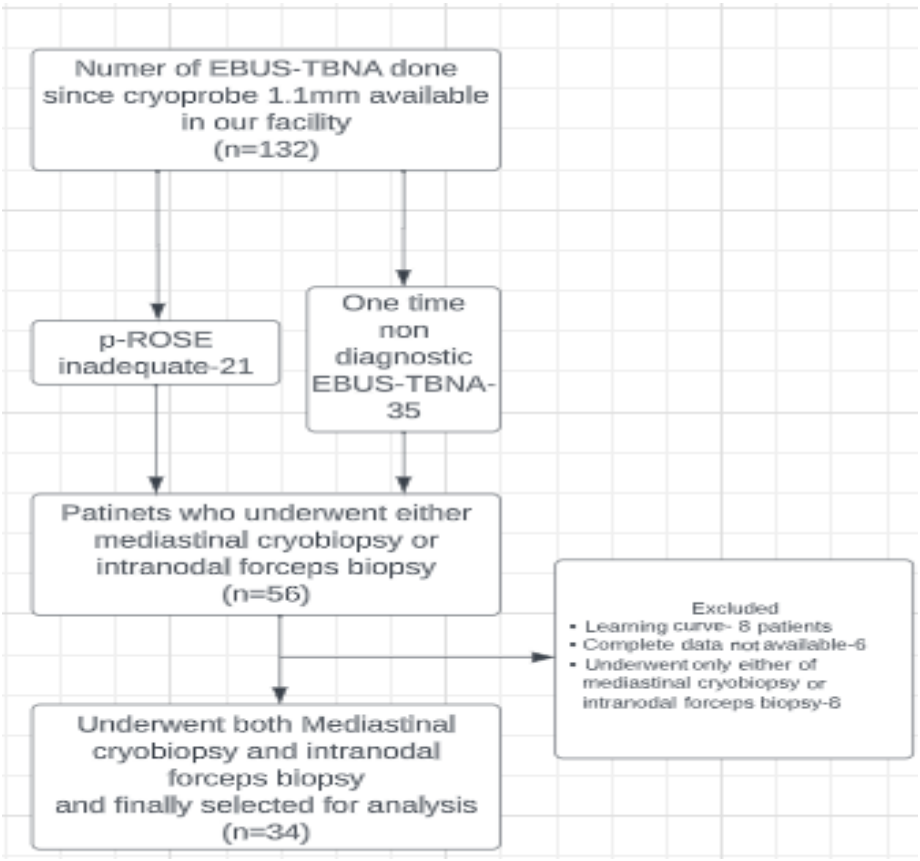

Figure 1. Consort diagram for selection of patients for analysis.

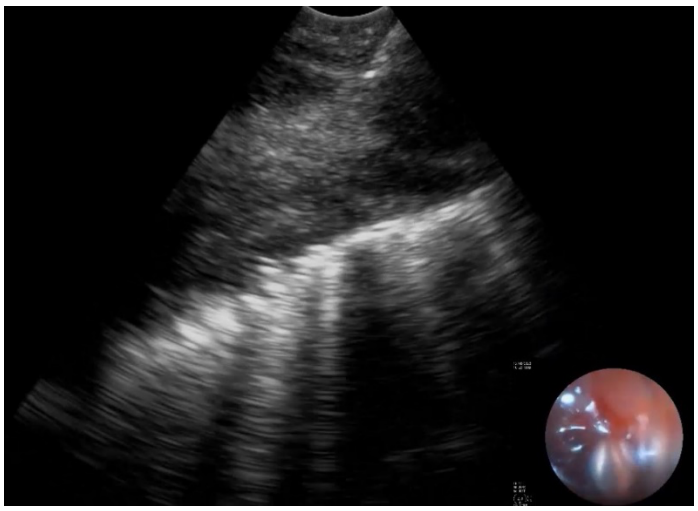

Figure 2. Transbronchial needle aspiration in the mediastinal lymph node through endobronchial ultrasound bronchoscope

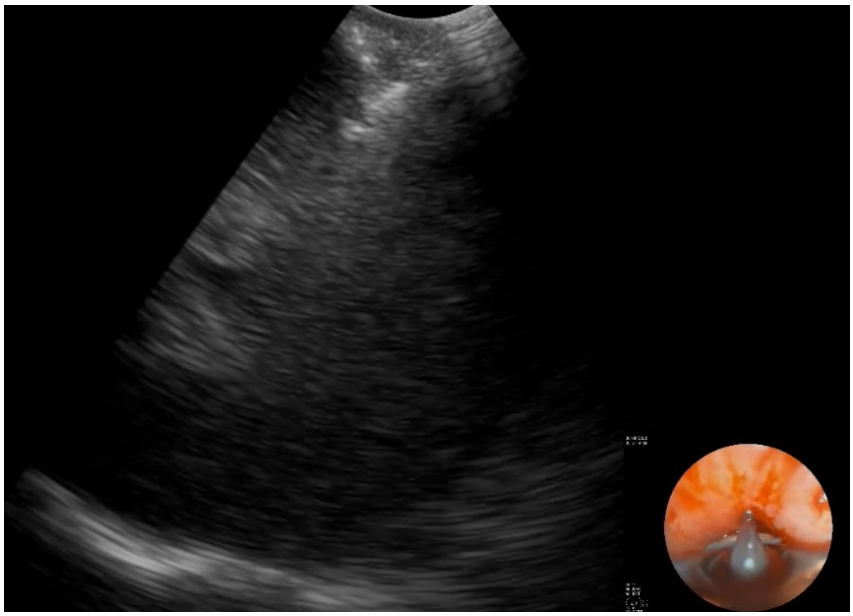

Figure 3. Cryoprobe in situ in the mediastinal lymph node through the Endobronchial ultrasound

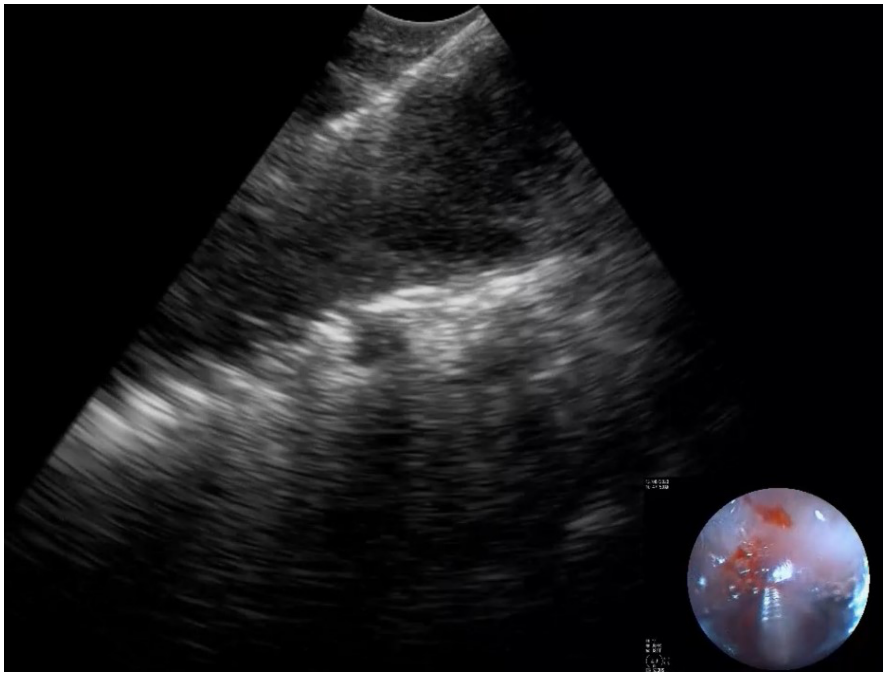

Figure 4. Intranodal biopsy forceps in situ in the mediastinal lymph node through the endobronchial ultrasound.

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 (%)	18 (52.9%)
EBUS-TBNA-n(%): EUS-B-FNA-n(%)	33 (97%): 1(3%)
Clinical indication- number. (%) Malignancy Tuberculosis Sarcoidosis Lymphoma	 15(44.1%) 9(26.4%) 9(26.4%) 1(2.9%)
Ultrasonographic characteristics- number. (%) >1cm Shape- Round Distinct Margins Heterogenous Coagulation necrosis present Conglomeration present Central hilar structure present Calcification present	 28(82.3%) 7(20.5%) 21(61.7%) 14(41.1%) 6(17.6%) 12(35.3%) 0 3(8.8%)

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

Yield data	EBUS-TBNA	EBUS-TBNA with mediastinal cryobiopsy	EBUS-TBNA with Intranodal forceps biopsy	p value
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