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, Kumar R, Ish P, et al. **Additional yield of transbronchial cryo-node biopsy over endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal lesions at a tertiary care center in India (COLD-FORCEPS-2 study).** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.3054

Additional yield of transbronchial cryo-node biopsy over endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal lesions at a tertiary care center in India (COLD-FORCEPS-2 study)

Manu Madan,[1] Rohit Kumar,[1] Pranav Ish,[1] Yash Kedia,[1] AJ Mahendran,[2] Rajnish Kaushik,[1] Neeraj Kumar Gupta,[1] Nitesh Gupta[1]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, VMMC and Safdarjung Hospital, Delhi, India; [2]SpR Transplant (lung) Medicine, Royal Brompton and Harefield Medicine, London, UK

Correspondence: Nitesh Gupta, Room no. 638, 6th Floor, SSB building, Department of Pulmonary Critical Care and Sleep Medicine, VMMC and Safdarjung Hospital, Delhi, New Delhi - 110029, India.
E-mail-niteshgupta2107@gmail.com

Contributions: all authors were involved in the literature search, planning, conducting, writing the original manuscript draft, literature search, and editing. All the authors have agreed with the submitted manuscript.

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

Ethics approval and consent to participate: institute ethical committee clearance taken vide S. No. IEC/VMMC/SJH/Project 2024-01/429 dated 4 March 2024.

Patient consent for publication: written informed consent has been taken from all patients or legally authorized representatives.

Funding: none.

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

Acknowledgments: residents and interventional pulmonology staff

Abstract

Endobronchial ultrasound (EBUS)-guided mediastinal cryobiopsy is a new modality for sampling mediastinal lymph nodes. The data regarding the diagnostic yield and utility of mediastinal cryobiopsy is still limited. Consecutive patients who were undergoing EBUS-guided transbronchial needle aspiration (EBUS-TBNA) were recruited in this study. We subjected the enrolled patients to EBUS-guided mediastinal cryobiopsy after obtaining their informed consent. The final diagnosis was made with a clinical-pathological-radiological assessment and clinical-radiological follow-up. A total of 101 patients were enrolled in the study. Adequacy in sampling achieved in EBUS-TBNA was 92.07%, compared to 98.01% achieved in EBUS-TBNA with mediastinal cryobiopsy. Diagnostic yields achieved in EBUS-TBNA and EBUS-TBNA with mediastinal cryobiopsy were 67.32% and 86.13%, respectively (p=0.001). EBUS patterns failed to predict the utility of mediastinal crobiopsy. No significant complications were observed. To conclude, EBUS-guided mediastinal cryobiopsy improves yield in patients undergoing 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, which yields a diagnosis in only about three-fourths of patients [1]. Mediastinal cryobiopsy can improve the diagnostic yield of EBUS-TBNA. Recently, it has garnered great enthusiasm among interventional pulmonologists.

Cryotherapy is a technique where tissue is rapidly frozen using a cryoprobe, and the removal of the cryoprobe leads to the extraction of the more extensive tissue, referred to as cryobiopsy [2]. Mediastinal lesions are sampled by mediastinal cryobiopsy using the same principle. Literature regarding the modality's potential has been scarce and conflicting to date. Although there are only a handful of randomized trials to date on the subject, and have found mediastinal cryobiopsy to be a helpful technique, the COLD-FORCEPS study, which was a retrospective study, did not find any significant difference between routine EBUS-TBNA and EBUS-TBNA along with mediastinal cryobiopsy groups [3-5]. The current study was conducted to evaluate the additional role of mediastinal cryobiopsy.

Materials and Methods

The study was a prospective study conducted in a tertiary care and referral facility. The study was initiated after approval from the institutional ethics committee. All patients with mediastinal lesions more than 0.5 cm in the short axis, undergoing EBUS-TBNA, were enrolled in the study after informed consent. All enrolled patients also underwent mediastinal cryobiopsy in addition to routine EBUS-TBNA.

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 a cricothyroid injection of lignocaine solution. A 19 or 21-Gauge needle (Olympus, Japan) was used for EBUS-TBNA. Glass slide-fixed smears and cell blocks were prepared. Aspirates were also processed for microbiological investigations, including staining for Mycobacterium tuberculosis smear, Xpert Mtb-RIF test, and Mycobacterial liquid cultures.

A diagnosis of tuberculosis was made if the microbiological investigation was favourable 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 tuberculosis. A diagnosis of malignancy was considered when cytopathological analysis of TBNA showed tumour cells. Per our hospital protocol, all patients were followed up for one month for a clinical-radiological response after the procedure, and a final diagnosis was made after one month of follow-up.

Experienced proceduralists performed all EBUS procedures. Four EBUS-TBNA passes were taken for all patients, from which TBNA smears, clot core samples, and microbiological samples were processed. After EBUS-TBNA, the site of EBUS-TBNA was localized, and an attempt to pass the 1.1mm miniature flexible cryoprobe (*ERBE, Medizintechnik, Tübingen, Germany)* through the port was made. In case of inability to penetrate the capsule of the lymph node with the cryoprobe, another port was created using a 19G/ 21G needle or an electrocautery knife for 1-second actuation. After the port creation, a cryoprobe was 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, two samples of each cryobiopsy were taken before concluding the procedure.

Statistical analysis

The demographic and procedural details were noted in Microsoft Excel, and patient reports and procedural videos were also stored in the department's system. 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 were as mean (SD) or median (IQR). The Chi-squared test was used to compare categorical variables.

Results

We screened 128 patients posted for EBUS-TBNA in our department. Amongst these, eighteen patients refused to undergo additional mediastinal cryobiopsy procedures, while another nine declined to consent to any study. Finally, we included 101 patients who underwent both EBUS-TBNA and mediastinal cryobiopsy procedures for final analysis. The consort diagram for the 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 the EBUS-TBNA procedure have been 98.01% and 86.13%, respectively. The current study yield is summarised in Table 2. All patients were sampled using the endobronchial approach. The number of passes taken for EBUS-TBNA was four passes for all patients. Two cryobiopsy samples were taken for all patients. The median size (range) of the clot core sample and cryobiopsy sample were 11 mm3 (3-38) and 8 mm3 (3-26), respectively. Cryobiopsy was done from the same port as EBUS-TBNA in 83 (83.16%) patients; new port creation was required in 18(17.8%) patients, while a new port using an electrocautery knife was done in 3(2.9%) patients.

The average procedure time, including patient preparation and observation, was 46.2 minutes. The most common lymph node sampled was subcarinal in 86 (85.14%) patients. In comparison, station 4R was sampled in 6 (5.9%) patients, 4L was sampled in 2 (1.9% each) patients and mediastinal masses were sampled in 7 (6.9%) patients. No significant complications were observed in any patients.

EBUS-TBNA with mediastinal cryobiopsy was superior to EBUS-TBNA or cryobiopsy alone (Tables 2 and 3). Mediastinal cryobiopsy is superior to EBUS-TBNA in diagnosing sinus histiocytosis (rare benign disorder) (Table 3). There were no ultrasonographic predictors of better diagnostic yield of mediastinal cryobiopsy, and cryobiopsy fared equally well for all diseases (Table 4). Ultrasonographic also did not predict patients in whom doing additional mediastinal cryobiopsy over and above EBUS-TBNA might yield better results; however, comparing diseases, sarcoidosis was significantly better picked up with EBUS-TBNA alone without doing a mediastinal cryobiopsy while Sinus Histiocytosis was only picked up in

mediastinal cryobiopsy, and was not picked up in EBUS-TBNA. There was also a significant trend toward diagnosing malignancy without doing a mediastinal cryo biopsy. However, this did not reach significance levels (Table 5).

On comparing the additional yield of mediastinal cryobiopsy over and above EBUS-TBNA, the yield of mediastinal cryobiopsy was significantly higher in tuberculosis and sinus histiocytosis as compared to malignancy (39.1% in tuberculosis vs 5.5% in malignancy, p=0.01 and 100%% in sinus histiocytosis vs 5.5% in malignancy, 0=0.001). It also seems to trend towards reaching significance in comparing tuberculosis and sarcoidosis (39.1% in tuberculosis vs 16.1% in sarcoidosis, 0=0.058) (*Supplementary Table 1*).

Discussion

Endobronchial ultrasound (EBUS) guided mediastinal cryobiopsy is a relatively new method. Researchers and interventional pulmonologists are interested in this procedure because of its sheer ability to increase yield without compromising its safety. Even though a recently published meta-analysis revealed the superiority of mediastinal cryobiopsy, only a few randomized trials exist [3-7].

An RCT by Zhang et al. of 197 patients, comparing EBUS-TBNA with cryobiopsy, found cryobiopsy to be superior (79.9% vs 91.8%, p=0.001) [3]. The order of doing cryobiopsy and TBNA did not affect the yield of the procedure. They used a criterion of size of more than 1 cm (short axis) for enrolment. In comparison, the other RCT by Fan et al. enrolled 271 patients and used similar enrolment criteria of size more than 1 cm [4]. They compared EBUS-TBNA alone with EBUS-TBNA combined with cryobiopsy and found that adding cryobiopsy to EBUS-TBNA was beneficial (81% vs 93% respectively, p=0.0039). Both studies found that cryobiopsy offers a significant advantage, especially in benign disorders, without reporting major complications.

A recently published RCT by Cheng et al, found that supplementing EBUS-TBNA with either intranodal forceps biopsy or mediastinal cryobiopsy lead to better diagnostic yield; however, comparing mediastinal cryobiopsy to intranodal forceps biopsy, mediastinal cryobiopsy was superior (85.7% vs 70.8%, p= 0.001) [7].

In the current study, all patients underwent routine EBUS-TBNA under conscious sedation followed by mediastinal cryobiopsy. We reported upfront EBUS-TBNA with cryobiopsy to be superior to EBUS-TBNA or mediastinal cryobiopsy alone, contrary to the COLD FORCEPS study [5]. The possible explanations for the difference can be, firstly, the COLD-FORCEPS study included only a sub-group of patients who were p-ROSE negative or had a previously inconclusive EBUS-TBNA procedure, EBUS-TBNA with mediastinal cryobiopsy was not the upfront procedure of choice. Thus, the two studies should be kept distinct. Secondly, even if

there was a difference between the two arms in the COLD-FORCEPS study, it could have been missed due to a small sample size study and a higher proportion of patients having lymph nodes of size less than 1 cm.

Additional analysis of this study shows that mediastinal cryobiopsy was better for diagnosing rare diseases like sinus histiocytosis and tuberculosis. However, most malignancy and sarcoidosis cases tend to be diagnosed in EBUS-TBNA alone. This is similar to the previous study, which suggested that mediastinal cryobiopsy has a better yield for diagnosing benign and rare diseases [3,4,6]. We also did not find the utility of endobronchial ultrasonographic features in predicting cryobiopsy yield.

Potential significant complications of the procedure include pneumothorax, pneumomediastinum, life-threatening bleeding, and mediastinal infection. However, no significant complications were noted in our patients. We found the procedure to be safe and effective in increasing diagnostic yield.

The strength of our study is that all patients and lymph nodes sampled were common in the two arms, thereby eliminating enrolment bias, which might be one of the significant limitations in a non-randomized study. Another strength of the current study is that EBUS-TBNA was protocolized and uniform. Also, our study did not exclude patients less than 1 cm in size, representing real-world data. There were a few limitations to the current research; the sample size was not powered enough to conclude factors predicting cryobiopsy success. In addition, pathologists were not blinded to the procedure done.

Conclusions

Adding EBUS-guided mediastinal cryobiopsy to routine EBUS-TBNA leads to a higher diagnostic yield. The diagnostic yield of mediastinal cryobiopsy is better in diagnosing rare and benign disorders.

References

1. Madan K, Mohan A, Ayub II, et al. Initial experience with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a tuberculosis endemic population. J Bronchology Interv Pulmonol 2014;21:208-14.
2. Lentz RJ, Argento AC, Colby TV, et al. Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. J Thorac Dis 2017;9:2186-203.
3. Zhang J, Guo JR, Huang ZS, et al. Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomized trial. Eur Respir J 2021;58:2100055.
4. Fan Y, Zhang AM, Wu XL, et al. Transbronchial needle aspiration combined with cryobiopsy in the diagnosis of mediastinal diseases: a multicentre, open-label, randomised trial. Lancet Respir Med 2023;11:256-64.
5. 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 2024. doi: 10.4081/monaldi.2024.2813. Online ahead of print.
6. Zhang Z, Li S, Bao Y. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy versus endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal disorders: a meta-analysis. Respiration 2024. doi: 10.1159/000538609. Online ahead of print.
7. Cheng TL, Huang ZS, Zhang J, et al. Comparison of cryobiopsy and forceps biopsy for the diagnosis of mediastinal lesions: a randomised clinical trial. Pulmonology 2024;S2531-0437(23)00240-4.

Online supplementary material

Supplementary Table 1. Comparison of disease-wise additional diagnostic yield of EBUS-TBNA guided mediastinal cryobiopsy over EBUS-TBNA.

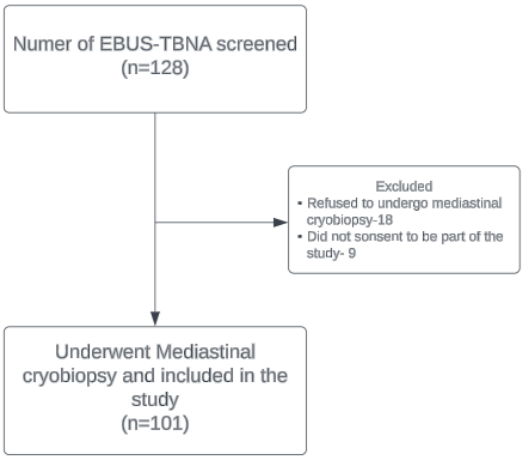

Figure 1. Consort diagram for selection of patients for analysis.

Table 1. Baseline characteristics of patients undergoing mediastinal cryobiopsy.

Characteristics	Patients (n=101)
Age(years) mean(±SD)	43.6(17.05)
Sex- Male (%)	57 (56.43%)
Clinical indication- number. (%) Malignancy Tuberculosis Sarcoidosis Lymphoma	 30(29.7%) 34(33.7%) 35(34.7%) 2(1.9%)
Ultrasonographic characteristics- number. (%) Size>1cm Shape- Round Distinct Margins Heterogenous Coagulation necrosis present Conglomeration present Central hilar structure present Calcification present	 80(79.2%) 32(31.7%) 66(65.3%) 45(44.6%) 12(11.9%) 16(15.9%) 19(18.9%) 2(1.9%)

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

Yield data	EBUS-TBNA	EBUS-TBNA with mediastinal cryobiopsy	p-value
Adequacy	92.07%	98.01%	0.052
Diagnosis yield	67.32%	86.13%	0.001

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

Table 3. Diagnostic yield of the EBUS TBNA vs. mediastinal cryobiopsy for various diagnoses.

Final diagnosis on Histopathology	EBUS-TBNA (n=101)	Mediastinal Cryobiopsy (n=101)	P value
Malignancy (n=18)	17 (94.5%)	14 (77.8%)	0.15
Tuberculosis (n=23)	14 (60.9%)	17 (73.9%)	0.35
Sarcoidosis (n=31)	26 (83.9%)	24 (77.4%)	0.52
Sinus Histiocytosis (n=3)	0	3 (100%)	0.02
Non-diagnostic	33 (32.6%)	32 (31.7%)	0.89

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

Table 4. Factors predicting better diagnostic yield of EBUS-TBNA guided mediastinal cryobiopsy.

	Positive diagnostic yield (n=69)	Negative diagnostic yield (n=32)	P value
Ultrasonographic features			
• >1cm	55 (79.7%)	25 (78.1%)	0.85
• Shape- Round	22 (31.9%)	10 (31.3%)	0.95
• Distinct Margins	44 (63.7%)	22 (68.8%)	0.61
• Heterogenous	33 (47.8%)	12 (37.6%)	0.33
• Coagulation necrosis present	5 (7.2%)	7 (18.8%)	0.08
• Conglomeration present	11 (15.9%)	5 (15.6%)	0.96
• Central hilar structure present	11 (15.9%)	8 (25%)	0.27
• Calcification present	1 (1.4%)	1 (3.1%)	0.56
Final Diagnosis on Histopathology			
• Malignancy (n=18)	14 (77.8%)	4 (22.2%)	0.001
• Tuberculosis (n=23)	17 (73.9%)	6 (26.1%)	0.001
• Sarcoidosis (n=31)	24 (77.4%)	7 (22.6%)	0.001
• Sinus Histiocytosis (n=3)	3 (100%)	0	0.02

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

Table 5. Factors predicting better additional diagnostic yield of EBUS-TBNA guided mediastinal cryobiopsy over EBUS-TBNA.

	Positive EBUS - TBNA diagnostic yield (n=68)	Negative EBUS-TBNA and positive mediastinal cryobiopsy diagnostic yield (n=19)	P value
Ultrasonographic features			
• >1cm	55 (80.8%)	14 (73.6%)	0.49
• Shape- Round	20 (29.4%)	7 (36.8%)	0.53
• Distinct Margins	46 (67.6%)	9 (47.3%)	0.10
• Heterogenous	33 (48.5%)	9 (47.3%)	0.92
• Coagulation necrosis present	10 (14.7%)	1 (5.2%)	0.27
• Conglomeration present	13 (19.1%)	1 (5.2%)	0.14
• Central hilar structure present	15 (22.1%)	2 (10.5%)	0.26
• Calcification present	1 (1.5%)	0	0.59
Final Diagnosis on Histopathology			
• Malignancy (n=18)	17 (94.4%)	1 (5.5%)	0.09
• Tuberculosis (n=23)	14 (60.9%)	9 (39.1%)	0.14
• Sarcoidosis (n=31)	26 (83.9%)	5 (16.1%)	0.001
• Sinus Histiocytosis (n=3)	0	3 (100%)	0.02

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