Clinical utility of endobronchoscopic ultrasound-guided fine-needle aspiration as the first modality of investigation in undiagnosed mediastinal lymph node in a TB-endemic country

Sir,

Mediastinal lymphadenopathy (ML) often presents with non-specific symptoms of fever, night sweat and weight loss. Granulomatous diseases and malignancies are the leading causes of ML.[1] Based on equivocal sensitivities demonstrated in multiple studies, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is now considered a replacement for mediastinoscopy.[2,3] In this prospective study, we aimed to determine the diagnostic yield and efficiency of EBUS-TBNA as the initial procedure in patients presenting with ML in an Indian setting where tuberculosis (TB) is endemic.

All patients suspected to be of benign or malignant aetiology who presented to the Department of Respiratory Medicine for evaluation of ML from July 2018 to June 2021 were included. Patients without informed consent for participating in this study were excluded. The study was approved by the Institutional Research Bureau (IRB). All the patients underwent EBUS-TBNA as an initial procedure. The standard technique for EBUS-TBNA was followed as described previously.[4] A linear echoendoscope (BF-UC160F, Olympus) was used to assess hilar and mediastinal lymph nodes. Rapid on-site evaluation (ROSE) of samples was employed for all the procedures. If a conclusive diagnosis was not obtained after processing all the specimens, a multidisciplinary team consisting of respiratory physicians, radiologists, pathologists and thoracic surgeons* (*as and when indicated) decided on further procedural workup or continued imaging surveillance. All patients on treatment and those needing further workup were on continued clinical follow-up for at least 6 months. The primary outcome was to evaluate the diagnostic accuracy and the overall yield of EBUS-TBNA in cases of ML.

Diagnosis of TB was made if there was bacteriological confirmation of presence of *Mycobacterium*

Table 1: Baseline demographics of the study patients

Characteristic	*N* = 322 (%/range)
Age, in years	58 (17–87)
Sex	
Male	198 (61.5)
Female	124 (38.5)
EBUS showing necrosis	98 (31)
Reactive	08 (8.2)
Malignancy	32 (32.7)
Granulomatous inflammation	58 (59.2)
EBUS echogenicity	
Hypoechoic	195 (60.6)
Isoechoic	90 (28)
Hyperechoic	37 (11.5)
Histopathology	
Non-small cell carcinoma	92 (51.1)
Adenocarcinoma	36 (20)
Squamous cell carcinoma	2 (1.1)
Adenosquamous	1 (0.6)
Not otherwise specified	17 (9.4)
Small cell carcinoma	13 (7.2)
Metastatic malignancy other than lung primary	10 (5.6)
Lymphoma	
Neuroendocrine tumours	4 (2.2)
Sarcoma	2 (1.1)
Mesothelioma	1 (0.6)
Spindle cell	1 (0.6)
Others	1 0.6)
Microbiology positivity	
AFB smear	4 (6.2)
AFB culture	16 (25)
GeneXpert	15 (4.7)

EBUS = endobronchial ultrasound

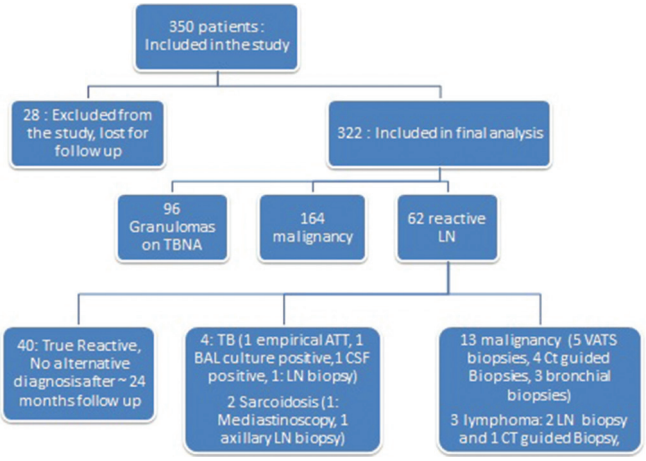

Figure 1: Flowchart of the study patients on EBUS-TBNA under conscious sedation for undiagnosed mediastinal lymph nodes EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration

tuberculosis (direct smear or culture or Xpert MTB Rif) and/or any of the following: (1) histopathology or cytology finding of caseating granulomas, (2) radiological findings consistent with TB, (3) clinical presentation consistent with TB with positive tuberculin test (>20 mm induration) with exclusion of other clinical considerations and (4) definite clinical and radiological improvement in 2 months of administration of exclusive anti-tubercular treatment.[5] Diagnosis of sarcoidosis was made when all the following criteria were present: (1) clinical–radiological presentation consistent with sarcoidosis, (2) non-necrotising epithelioid cell granulomas on histopathology or cytology, along with no Acid Fast Bacilli (AFB) on Ziehl–Neelsen stain and no growth of Mycobacteria Growth Indicator Tube (MGIT) and (3) clinicoradiological response after treatment with glucocorticoids.[6] Malignancy was diagnosed when cytology or histopathology confirmed diagnosis of malignancy.[7]

Table 2: Results after ROSE, cell block and actual final diagnosis of included patients

Diagnosis and method	*N* = 322 (%)
ROSE* diagnosis	
Reactive	74 (23)
Malignancy	161 (50)
Granulomatous inflammation	87 (27)
Final diagnosis (EBUS) after cell block	
Reactive	062 (19.3)
Malignancy	164 (50.6)
Granulomatous inflammation	096 (30.1)
Final diagnosis of the patients	
Reactive	40 (12.4)
Malignancy	180 (55.9)
Granulomatous inflammation	102 (31.7)
TB	64 (62.7)
Sarcoid	38 (37.3)
Out of 62 reactive/inconclusive EBUS, the final diagnosis was	
True reactive	40
Malignancy	16
Granuloma	06

*ROSE: Rapid On Site Evaluation

A total of 350 patients underwent EBUS-TBNA during the study period. A flowchart of the study patients is shown in Figure 1. Out of 350 patients, 322 were included in the final analysis. Baseline demographics and EBUS features of the study cohort are shown in Table 1. EBUS-TBNA correctly determined the final diagnosis in 300/322 cases with a yield of 93% (95% confidence interval [CI], 89%–95%). The negative predictive value (NPV) was 64.5% (95% CI, 55%–73%), and the diagnostic accuracy was 92.29% (95% CI, 89%–95%). Out of 260 patients who had a definitive diagnosis by EBUS-TBNA, 164 were malignant and 96 were granulomatous. EBUS-TBNA successfully diagnosed sarcoidosis in 36/38 (95%) patients and TB in 60/64 (94%) patients. EBUS-TBNA cultured *Mycobacterium tuberculosis* in 16 (25%) of 64 cases who had a final diagnosis of TB. EBUS-TBNA was able to clinch lymphoma diagnosis in 7/10 patients and prevented the need for more invasive procedures.

Sixty-two patients had a diagnosis of reactive lymphnode (LN) on EBUS-TBNA, and 40 of them were found to be 'true reactive' on clinical and imaging follow-up. Of the remaining 22 patients, 16 and six had malignancy and

Table 3: Comparison of the current study with previous studies

Study	n	Inclusion criteria	Reference standard	Results				Safety
				S	SP	PPV	NPV	
Hwangbo *et al*.[10]	61	Confirmed or suspected lung cancer	Malignancy: pathological confirmation of malignancy by any tissue sampling method (EBUS-TBNA, EUS-B-FNA or surgical biopsy); benign disease: surgical confirmation of lesions showing no malignant disease	84.4	100	100	93.3	NA
Herth *et al*.[11]	139	Confirmed or suspected lung cancer	Malignancy: positive cytological result of malignancy accepted as evidence of cancer; benign disease: confirmed by open thoracotomy, thoracoscopy or clinical follow-up over 6–12 months	91.5	100	100	91.8	NA
Lee *et al*.[12]	37	Confirmed or suspected lung cancer	Malignancy: defined by pathological confirmation via EBUS-TBNA, EUS-B-FNA, mediastinoscopy or mediastinal lymph node dissection; benign disease: confirmed by surgery	79.3	100	100	57.1	NA
Oki *et al*.[13]	146	Confirmed or suspected lung cancer	Malignancy: positive findings from the needle aspiration procedure were regarded as true-positive; benign disease: confirmed by lack of lymph node progression on CT over 6 months	51.5	100	100	87	NA
Present study	322	Diagnosis or staging of lung cancer or evaluation of mediastinal or hilar adenopathy >1 cm in size	Positive cytologies regarded as final diagnosis Benign results confirmed by surgery (n = 54) or clinical follow-up (n = 51)	91.8	100	100	71.4	No serious complications

CT = computed tomography, EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration, NPV = negative predictive value, PPV = positive predictive value, S = sensitivity, SP = specificity, EUS-B-FNA: Endoscopic ultrasound guided bronchial fine needle aspiration

granulomatous inflammation, respectively. The final diagnosis was obtained through various alternative methods, as shown in Figure 1.

Subgroup analysis showed EBUS-TBNA had a sensitivity of 92 (95% CI, 87–95) and NPV of 71 (95% CI, 61–80) in malignancy. EBUS-TBNA had a sensitivity of 94 (95% CI, 88-95), NPV 87 (95% CI, 75–93), specificity 98 (95% CI, 88–99.9) and positive predictive value (PPV) 99 (95% CI, 93–99.8) in diagnosing TB. ROSE was able to clinch diagnosis in 161/164 and 87/96 patients with malignancy and TB, respectively [Table 2]. EBUS-TBNA was diagnostic for TB in 60 of 64 (94%) cases in this study. Of these, 16 (25%) were culture positive. Other studies from TB-endemic countries describing the use of EBUS-TBNA for diagnosis of mediastinal tuberculous lymphadenitis report sensitivity for culture-positive diagnosis to be from 38% to 46% and for a composite microbiological and clinicopathological diagnosis to be from 69% to 86%.[4,7-9] Sensitivity of EBUS-TBNA in diagnosing TB in the current study was consistent with that of a larger multicenter cohort of patients. However, the culture positivity of 25% was much lower than 47% found in that study.[4] Low bacillary load in the specimen might be the reason behind the lesser culture positivity found in the present study. ROSE was able to identify the correct pathology in 248/260 (95%) patients. Granulomatous inflammation was more difficult to pick up on ROSE, and 9/12 patients who were ROSE negative had granulomas on the cell block.

All procedures were done under conscious sedation, and no severe complications were observed post-procedure. Five patients had persistent hypoxia and required in-hospital observation for 24 h. The rest of the patients were discharged after 2 h of post-procedure observation. We compared the data on EBUS-TBNA in diagnosing malignancy in the current study to the available literature [Table 3] and found that sensitivity was very similar to that of previously published data.[10-13] NPV in all the studies was quite variable and hence non-comparable. One of the reasons for this can be selection bias and differences in the prevalence of malignancy in different practice setups.

In conclusion, EBUS-TBNA was a safe, highly sensitive procedure that could be done under conscious sedation. It had similar sensitivity and NPV in diagnosing TB as well as malignancy. EBUS with ROSE had more yield in malignancy than granulomas. EBUS should be 'the initial investigation' of choice in patients with undiagnosed ML.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Submitted: 28-Mar-2022 **Revised:** 26-Apr-2022
Accepted: 01-May-2022 **Published:** 25-Oct-2022

REFERENCES

1. Vaidya PJ, Kate AH, Chhajed PN. Endobronchial ultrasound-guided transbronchial needle aspiration: The standard of care for evaluation of mediastinal and hilar lymphadenopathy. J Cancer Res Ther 2013;9:549-51.
2. Navani N, Spiro SG, Janes SM. Mediastinal staging of NSCLC with endoscopic and endobronchialultrasound. Nat Rev Clin Oncol 2009;6:278-86.
3. Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: A systematic review and meta-analysis. Eur J Cancer 2009;45:1389-96.
4. Herth FJ, Eberhardt R, Vilmann P, Krasnik M. Ernst a real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax 2006;61:795-8.
5. Light RW. Pleural Diseases. Baltimore: Lippincot, Williams and Wilkins; 2001. p. 151-81.
6. Gupta N, Muthu V, Agarwal R, Dhooria S. Role of EBUS-TBNA in the diagnosis of tuberculosis and sarcoidosis. J Cytol 2019;36:128-30.
7. Oki M, Saka H, Kitagawa C, Tanaka S, Shimokata T, Kawata Y, *et al*. Real-time endobronchial ultrasound– guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. Respirology 2007;12:863-8.
8. Navani N, Nankivell M, Woolhouse I, Harrison RN, Munavvar M, Oltmanns U, *et al*. Endobronchial ultrasound–guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: A multicenter study. J Thorac Oncol 2011;6:1505-9.
9. Steinfort DP, Conron M, Tsui A, Pasricha SR, Renwick WE, Antippa P, *et al*. Endobronchial ultrasound–guided transbronchial needle for the evaluation of suspected lymphoma. J ThoracOncol 2010;5:804-9.
10. Hwangbo B, Lee GK, Lee HS, Lim KY, Lee SH, Kim HY, *et al*. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. Chest 2010;138:795-802.
11. Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. Chest 2010;138:790-4.

12. Lee KJ, Suh GY, Chung MP, Kim H, Kwon OJ, Han J, *et al*. Combined endobronchial and transesophageal approach of an ultrasound bronchoscope for mediastinal staging of lung cancer. PLoS One 2014;9:e91893.
13. Oki M, Saka H, Ando M, Kitagawa C, Kogure Y, Seki Y. Endoscopic ultrasound-guided fine needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration: Are two better than one in mediastinal staging of non-small cell lung cancer? J Thorac Cardiovasc Surg 2014;148:1169-77.

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Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_189_22

How to cite this article: Mehta AA, Perathur A, Paul T, Divya S, Sudhakar N, Vallonthaiel AG, *et al*. Clinical utility of endobronchoscopic ultrasound-guided fine-needle aspiration as the first modality of investigation in undiagnosed mediastinal lymph node in a TB-endemic country. Lung India 2022;39:583-6.