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Original Article

Internal Medicine Section

EBUS- TBNA-Initial Experience from a Tertiary Care Center in Southern India

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ABSTRACT

Introduction: Conventional trans bronchial needle aspiration is associated with a low diagnostic yield in mediastinal adenopathy. Ultra sound guidance improves the diagnostic yield in these cases. Though linear probe EBUS was introduced in southern India as early as 2008, there is a dearth of literature in South Indian population on the utility of this diagnostic modality.

Aim: To analyse the diagnostic yield, sensitivity, specificity of real time endo bronchial ultrasound guided trans bronchial needle aspiration (EBUS-TBNA).

Materials and Methods: A prospective observational study was carried out from April 2014 to October 2016. Patients referred for evaluation of medisatinal lymphadenopathy were evaluated with computed tomography of the thorax and EBUS-TBNA was done under conscious sedation. Rapid on site examination was done. A sample that was positive for malignant cells/ granuloma was considered to be diagnostic. A non-diagnostic procedure was followed up with definitive surgery or a six month clinicoradialogical follow up.

Results: The study included 78 patients (48 males) with mean age 55.9 years. EBUS-TBNA detected 237 enlarged mediastinal nodes with average diameter of 20.48±8.55 mm. A total of 125 lesions were sampled of which sub carinal lymph node was the most common station (44.8%). Average of 1.6 lymph nodes was sampled per patient with 2.92 passes per lymph node. The procedure had a diagnostic yield of 91.02%, with sensitivity of 89.55% (79.65-95.70%), specificity of 100% (71.51-100%), Negative likelihood ratio of 0.10 (0.05-0.21), positive predictive value of 100% (94.04-100%), negative predictive value of 61.11% (32.75-82.70%). Majority of the patients were diagnosed with non small cell cancer with tuberculosis constituting the major diagnosis among the patients with clinical suspicion of a non malignant aetiology. There were no complications associated with the procedure.

Conclusion: EBUS guided TBNA is a safe procedure with a good diagnostic yield. It is a useful procedure in lymph nodes which remain inaccessible by conventional TBNA or mediatinoscopy based on size or location.

Keywords: Malignancy, Mediastinal adenopathy, Tuberculosis

INTRODUCTION

India is a country with high prevalence of tuberculosis as well as lung malignancy [1,2]. Many of these patients present with mediastinal lymphadenopathy raising a diagnostic dilemma of the treating physician. Conventional TBNA (Transbronchial needle aspiration) and mediastinoscopy are diagnostic diagnostic yield of approximately 42-55% [3,4]. Mediastinoscopy had a sensitivity of 81.8% a specificity of 100%, for the detection of mediastinal lymph node [5].

Though mediastinoscopy has a high specificity, it requires general anaesthesia, long hospital stay and is available only in specialized centers. Conventional TBNA is traditionally used in these cases. Mediastinoscopy has access mainly to the mediastinal lymph nodes. EBUS- TBNA can however be performed as an outpatient procedure under local anaesthesia and conscious sedation. EBUS has access to mediastinal and hilar lymph nodes. EBUS-TBNA is therefore, a promising tool for diagnosis of mediastinal adenopathy in a developing country like India. Though Southern India pioneered this technology in India, there is a dearth of original studies in the south Indian population.

The aim of the study was to assess the diagnostic yield, sensitivity, and specificity of EBUS-TBNA in patients with Computed Tomography (CT) proven mediastinal adenopathy from a tertiary care center in Southern India.

MATERIALS AND METHODS

This was a prospective observational study carried out from April 2014 to October 2016 in a tertiary care university hospital. Institutional ethics board approval was confirmed (IEC-AIMS-2016-PULM-137).

Patients referred to the Department of Pulmonary Medicine for evaluation of mediastinal adenopathy were enrolled for the study. All patients were subjected to thoracic CT for evaluation for mediastinal adenopathy using standard 3 mm staging CT chest protocols.

A detailed history, physical examination, radiological findings and provisional clinical diagnosis was recorded after an informed consent. Lymph nodes were considered enlarged when the short axis nodal diameter on CT chest was >1 cm, and classified using the International Association for the Study of Lung Cancer (IASLC) classification [6]. All patients were given nebulized lignocaine (4% solution) immediately before the procedure. Procedure was done under conscious sedation with intravenous midazolam and fentanyl. Endobronchial ultrasonography was conducted using a video ultrasound bronchoscope (CP-EBUS; BF-UC 180F using the EU-ME2 Ultrasound system; EVIS EXERA III Series CV190 Video Processor; Olympus Medical Systems, Tokyo, Japan). The location, shape, and structure of the lesions were examined with ultrasound. The best view of the node was identified on EBUS and dimension of the lymph nodes were documented by measuring the short axis diameter of the nodes. TBNA was done under real-time ultrasound guidance using a dedicated, disposable, 22-gauge, Vizishot needle (NA-201SX-4022 Olympus Medical Systems, Singapore). A single needle was used for accessing target stations. A non suction syringe technique was used wherein the stylet was partially withdrawn rapidly when within the target node to create intrinsic suction. The needle was moved back and forth 15-20 times and finally retracted back within the sheath and the needle assembly was unlocked and withdrawn from the EBUS Scope for cytological assessment. Between 3 to 5, passes were taken from each nodal station with the sequence of assessment being N3 followed by N2 and N1 where

applicable. The primary focus of the assessment was diagnosis rather than staging. On-site cytological assessment for adequacy of the sample was carried out by a dedicated cytopathologist. Adequate lymph node samples were defined by preponderance of lymphocytes which represented a successful procedure. Malignancy was diagnosed based on the representative samples containing malignant cells. Sarcoidosis was diagnosed in cases with compact epithelioid cell granuloma without necrosis and negative Acid-Fast Bacilli (AFB) smears with compatible clinicoradiological features. Smears were considered diagnostic of Tuberculosis (TB) in the presence of extensive necrotizing granulomas and/or demonstration of AFB or positive MTB PCR. In patients with suspected TB, the aspirates were also sent for mycobacterial cultures by the BACTEC when possible.

A sample that was positive for malignant cells/granuloma was considered to be diagnostic, dispensing with another surgical biopsy. Non diagnostic EBUS-TBNA bronchoscopy was followed up with a definitive diagnostic procedure (surgery by video assisted thoracoscopy or by mediastinoscopy) that is defined as the reference standard. Cases which were not diagnosed by all (bronchoscopic or surgical) methods, a six month or longer, chest CT follow up was defined as the reference standard.

STATISTICAL ANALYSIS

Data was recorded in a database designed in Microsoft Office Excel 2010. Diagnostic yield, sensitivity, specificity, positive predictive value, negative predictive value was computed using appropriate equations.

RESULTS

Seventy eight patients were included in the study in which 30 were females and 48 were males. Mean age of the study population was 55.9 years (range-17-85 years) [Table/Fig-1]. Six cases were done under general anaesthesia while rest of the cases was done under local anaesthesia and conscious sedation.

Characteristic	
Age (mean±SD)	55.9±15.4 years
Males	48 (61.53%)
Females	30 (38.46%)
Clinical suspicion	
Infection/Granulomatous disorder	34
Malignancy	43
Others	1

[Table/Fig-1]: Baseline demographic characteristics.

[Table/Fig-2] shows the bronchoscopic characteristics of the study population. Two hundred and thirty seven enlarged mediastinal lymph nodes were identified by EBUS of which 125 were sampled by ultrasound guided transbronchial needle aspiration. Subcarinal lymph was the most commonly enlarged lymph node as well the one frequently subjected to aspiration.

Needle wash cytology was done in 34 cases in which two cases were positive for malignant cells. MTB-PCR was done in 16 cases in which two cases were positive for *Mycobacterium tuberculosis*.

BACTEC culture grew *Mycobacterium tuberculosis* in two cases and non tuberculous mycobacteria in two cases. One case in which non tuberculous mycobacteria was grown was proven to be a case of small cell neuroendocrine tumour on cytology and the other case was diagnosed as sarcoidosis.

As shown in [Table/Fig-3] non small cell lung cancer was the most common diagnosis in this study. This included four cases of squamous cell carcinoma, eight cases of adenocarcinoma and six cases of non-small cell cancer. Among the non malignant diseases tuberculosis was more prevalent. Of the 43 cases evaluated for malignancy 33 cases were diagnosed to be malignant, four cases were taken as false negative and six cases were taken are true negative. Two patients with negative EBUS cytology were later proven to have lymphoma through VATs guided lymph node biopsy. One case of Non small cell lung cancer subjected to EBUS to rule out progressive disease had negative cytology. He died on follow up and hence taken as a false negative. One patient with pancreatic cancer with suspected lung metastasis had granuloma on EBUS cytology was lost to follow up was taken as false negative.

One patient with a granuloma, two patients with reactive lymph nodes, three patients with no evidence of sarcoidosis, tuberculosis, malignancy on microbiology and cytology showed no progression of disease on six month follow up and were hence taken as true negative.

Characteristics	Number
Number of lymph nodes enlarged	237
2R	3 (1.26%)
2L	2 (0.84%)
4R	46 (19.4%)
4L	30 (12.66%)
7	59 (24.89%)
10R	15 (6.33%)
10L	7 (2.95%)
11R	48 (20.25%)
11L	27 (11.39%)
Diameter of lymph nodes (mean±SD)	20.48±8.55 mm
Number of lymph nodes sampled	125
2R	1 (0.8%)
2L	1 (0.8%)
4R	23 (18.4%)
4L	11 (8.8%)
7	56 (44.8%)
10R	3 (2.4%)
10L	1 (0.8%)
11R	17 (13.6%)
11L	10 (8%)
Right upper lobe mass	1 (0.8%)
Right paratracheal mass	1 (0.8%)
Average number of lymph nodes sampled per patient	1.6
Average number of passes	365
Average number of passes per patient	4.67
Average number of passes per lymph node	2.92

[Table/Fig-2]: Bronchoscopic characteristics.
2R-right upper paratracheal lymph node; 2L-left paratracheal lymph node; 4R- right lower paratracheal lymph node; 4L-left lower paratracheal lymph node; 7- subcarinal lymph node 10 R-right hilar 10 L-left hilar; 11R-right interlobar; 11L-left interlobar

Malignant	
Small cell carcinoma	6
Non small cell carcinoma	18
Small cell neuroendocrine tumour	1
Round cell s/o lymphoproliferative disorder	1
Poorly differentiated malignancy	2
Metastatic cancer	5
Non malignant	
Tuberculosis	16
Sarcoidosis	11
Reactive lymph node	5
Granuloma	2
Negative for malignancy/TB/sarcoidosis	11

[Table/Fig-3]: Diagnosis obtained through EBUS-TBNA.

Among the 35 cases evaluated to rule out non malignant disorders, 16 cases were diagnosed as tuberculosis, 11 cases were diagnosed as sarcoidosis.

Diagnosis of tuberculosis was based on positive BACTEC culture alone in one patient, positive BACTEC culture with consistent histology in one patient, positive MTB-PCR with consistent cytology in two patients, cytology with positive mantoux test and response to ATT in 13 patients. Eleven cases were diagnosed as sarcoidosis based on cytology, elevated ACE levels, negative Mantoux and clinical response to treatment.

One patient with gingival malignancy with paratracheal lymph nodes had no evidence of tuberculosis or malignancy in EBUS cytology. Patient was later subjected to VATS biopsy which showed a granuloma. One patient with reactive lymph nodes on EBUS cytology was diagnosed as sarcoidosis on follow up. EBUS failed to yield a diagnosis in a patient with suspected neurofibroma. Five patients in whom EBUS cytology showed no evidence of granuloma or malignant cells were followed up for six months. There was no evidence of progression of disease in these patients and hence the result was taken as true negative.

The diagnostic yield, sensitivity and specificity was similar in the malignant and the non malignant group [Table/Fig-4].

	Total	Malignant	Non malignant
Diagnostic yield (%)	91.02%	90.69%	91.42%
Sensitivity (%)	89.55% (79.65-95.70%)	89.19% (74.58-96.97%)	90.00% (73.47-97.89%)
Specificity (%)	100% (71.51-100%)	100 (54.07-100%)	100% (47.82-100%)
Negative likelihood ratio	0.10 (0.05-0.21)	-0.11 (0.04-0.27)	0.10 (0.03-0.29)
Positive predictive value	100% (94.04-100%)	100 (89.42-100%)	100% (87.23%-100%)
Negative predictive value	61.11% (32.75-82.70%)	60.00% (26.24-87.84%)	62.5% (24.49 -91.48%)

[Table/Fig-4]: Results of the study.

The procedure was not associated with any significant complications; specifically there were no serious adverse events like pneumothorax, inadvertent major vessel injury, or severe bleeding requiring hospitalization or intensive care monitoring. Bleeding was minimal in most cases and the procedure was well tolerated.

DISCUSSION

Endobronchial ultrasound is a powerful weapon in the diagnostic armamentarium of the pulmonologist. EBUS guided TBNA has been extensively used for diagnosis and staging of malignancy in developed countries. Primary aim of this analysis is to look into the results of this technology newly introduced in our institution.

In the present study, 55.18% of the cases were evaluated with a clinical suspicion of malignancy and rest of the cases was evaluated for benign disorders like tuberculosis and sarcoidosis. This reflects the change in the trend of the cases of mediastinal adenopathy coming to the Indian pulmonologist. Previously tuberculous lymphadenopathy constituted a major diagnosis in the Indian setting, and it was not uncommon to start a patient with mediastinal adenopathy with positive Manotux test on empirical ATT. The proportion of cases with malignancy in this study point to the need for conclusively establishing a histological/microbiological diagnosis before starting the treatment of the patient.

On an average 1.6 lymph nodes were sampled per patient. In the study by Yasufuku K et al., at least 3 lymph nodes are to be sampled for staging of lung cancer [7]. But the aim of our study was a diagnosis rather than staging of lung cancer, with the highest station being considered for EBUS-TBNA.

Each lymph node was subjected to 2.92 needle passes. Number of needle passes required for a definite diagnosis is still under debate. Our findings support limiting the number of needle passes to three per lymph node. This in agreement with the findings of the study by Lee HS et al., [8].

Needle wash cytology is a technique which adds to the diagnostic yield in FNA of thyroid and breast [9,10]. Cytology of bronchial biopsy rinse fluid has shown to increase the diagnostic yield for lung cancer [11]. Needle wash cytology is routinely performed after TBNA on the basis of these evidence. But this study demonstrates that needle wash cytology adds very little to the diagnostic yield, as it was positive in only 5% of the cases.

Tuberculosis was diagnosed in 12.5% cases based on positive MTB- PCR and 12.5% was diagnosed based on positive culture. Thus 25% of the patients diagnosed as tuberculosis had a positive microbiological evidence of tuberculosis. In the study by Dhamija A et al., 55% of tuberculosis cases had a positive microbiological evidence [12]. Fewer cases with microbiological evidence of tuberculosis point to the paucibacillary nature of mediastinal tuberculosis in this part of the country.

There is a greater preponderance of malignant disorders compared to non malignant aetiology of mediastinal adenopathy in this series. This is data is similar to that in studies from East Asia and Europe [13,14] but contrast to the Indian data [12,15] in which granulomatous disorders constitute the most common diagnosis. This may be due to different health profile of the Kerala population compared to the rest of India.

	Diagnostic yield (%)	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Ye T et al., [16]	97.2	95.08	100	100	93.02
Herth FJ et al., [14]	93	94	100	100	11
Cetinkaya A et al., [17]	92	90.8			61.7
Dhamija A et al., [12]	88				
Gahlot T et al., [18]	92				
Madan K et al., [19]	74.5	81.7	100	100	22.73
Sorhaug S et al., [20]	82.4	94.9			81.2
Present study	91.02	89.55	100	100	61.11

[Table/Fig-5]: Comparison of results with similar studies [12,14,16-20].

The diagnostic yield, sensitivity, specificity, positive predictive value, negative predictive value of this study is compared with other similar studies is shown in [Table/Fig-5] [12,14,16-20].

The diagnostic yield of this study is less than the study by Ye T et al., [16] similar to results by Herth FJ et al., Cetinkaya E et al., and Gahlot T et al., [14,17,18], but better compared to the study done by Dhamija A et al., [12]. The sensitivity, specificity, positive and negative predictive value is comparable to similar studies [14,16,17]. No significant complication was seen associated with the procedure. More over most of the cases were done on a day case basis under local anaesthesia and conscious sedation. This may help in cutting down the cost of treatment, hospital stay and improves the patient satisfaction. But cost factor, hospital stay and patient satisfaction has not been studied in the current protocol. Further large scale studies are required on the cost effectiveness of EBUS-TBNA in a resource limited setting like India.

LIMITATION

Our study was not without its limitations. Our sample size is small compared to other similar studies, but comparable in terms of

quality of yield and diagnostic accuracy to larger western datasets. The study being done in referral teaching hospital would not reflect the disease prevalence in the general population.

CONCLUSION

EBUS-TBNA with its good diagnostic yield, sensitivity, specificity, in both benign and malignant disorders at a low complication rate is promising tool in a developing country like India where there is a high prevalence of granulomatous disorders as well malignancy of the lung.

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