

ORIGINAL RESEARCH

Role of endobronchial ultrasound guided transbronchial needle aspiration {ebus-tbna} for diagnosis of mediastinal and hilar lymphadenopathy: A descriptive observational study

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ABSTRACT

Background: Enlargement of intrathoracic lymph nodes can be due to a number of causes including infection, inflammation, neoplastic or just nonspecific reactive hyperplasia. Patients with mediastinal lymphadenopathy require accurate diagnosis to determine optimal treatment. In 2002, convex probe endobronchial ultrasound {CP-EBUS} was developed to perform real time endobronchial ultrasound guided transbronchial needle aspiration {EBUS-TBNA}. This is used to obtain cytological and histological samples of lesions. This procedure is highly safe and accurate for the examination and staging of mediastinal and hilar lymph nodes. **Methods:** An observational study on 55 patients of mediastinal and/or hilar lymph nodes who were subjected to EBUS-TBNA was conducted to assess the diagnostic yield and safety of this procedure. **Results:** There were 36.4% females and 63.6 % males with most patients from 61-70 years age group (29.1%) followed by 41-50 years (18.2%). There was a history of Tuberculosis in 7 patients (12.7%) and all were HIV negative. Majority of the patients had single lymph node (81.8%) while 18.2% had multiple lymph nodes. TB was the most common diagnosis in 30.9%, followed by reactive Lymphadenopathy in 29.1 %, malignancy in 23.6% and others in 14.5% cases. Total 26 cases had complications (47.3%), out of which most common was minor bleeding in 17 cases (30.9%), followed by bleeding in 4 cases (7.3%), post-procedure fever in 2 cases (3.6 %). One case had fever, hoarseness of voice and ventricular premature beats (1.8%) each. **Conclusion:** EBUS-TBNA is a safe procedure for getting tissue diagnosis with minimal invasion in mediastinal and hilar lymphadenopathy. However, the procedure requires expertise.

Keywords: EBUS-TBNA, Mediastinal Lymphadenopathy, Hilar Lymphadenopathy, Tuberculosis

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INTRODUCTION

Applications of Bronchoscopic needle aspiration have been expanded to include not only sampling of paratracheal or mediastinal lymph nodes, but also to assess peripheral, parenchymal, submucosal and endobronchial lesions.(1)The procedure allows for sampling through the trachea or bronchial wall and sampling of tissue beyond the vision of the operator.(2)

TBNA was introduced and performed by Dr Eduardo Schieppati in 1949 with rigid bronchoscope. In 1978, Wang et al designed a prototype needle for flexible bronchoscope.(3) In 2002, convex probe endobronchial

ultrasound (CP-EBUS) was developed with the ability to perform real time endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA).(4)

Real time endobronchial ultrasound guided transbronchial needle aspiration combines endoscopic visualisation with high frequency ultrasound imaging, which is used to obtain cytological and histological samples of lesions. This procedure is safe and highly accurate for the examination and staging of mediastinal and hilar lymph nodes in patients with known or suspected lung malignancy.(5)

EBUS-TBNA provides high diagnostic sensitivity and specificity for TB lymphadenitis and sarcoidosis

(72.4% vs 71.4 % and 100.0 % vs 10.00 %, respectively). Diagnostic yield of EBUS-TBNA was ~80 % for detection of sarcoidosis. (6)

We undertook this study to assess the role of EBUS-TBNA in obtaining adequate samples for diagnosing hilar and mediastinal lymphadenopathy and also to assess the safety of this procedure.

MATERIALS AND METHODS

This study was conducted in a tertiary care hospital in Pune over a period of 2 yrs. Recruitment into the study started after approval from the hospital Ethics Committee. This was a descriptive observational study. A total of 55 cases were studied. A written and informed consent was obtained from all patients.

Patients with hilar and/or mediastinal lymphadenopathy of size more than 10 mm in long axis on CT chest or PET CT and above 18 years of age were included. Those with coagulopathy, unstable cardiovascular or hemodynamic status, pregnant patients were excluded.

EBUS guided TBNA was performed with 22-gauge needle under ultrasound and color doppler guidance

with an EBUS bronchoscope under conscious sedation. Lymph node stations and numbers were determined according to the 7th edition of the International Association of the Study of Lung Cancer Classification (6). EBUS-TBNA was performed through the bronchus.

In each patient, the largest and/or most hypochoic lymph node was targeted. A smear of samples was prepared on a slide and it was fixed in 95% alcohol, Papanicolaou stain and air-dried in May-Grunwald Giemsa stain. Ziehl-Neelsen staining was also performed and samples were sent for culture of Mycobacterium.

STATISTICAL ANALYSIS

Data was collected using a semi structured pretested questionnaire and was entered in Microsoft Excel. Data was represented in frequencies and percentages. Mean and standard deviation of quantitative variables was taken. Chi-square test was used for association and student's t-test used for comparison between the study variables. Significance was considered at p<0.05.

RESULTS

Table 1: Gender Distribution

Gender	Number	Percent
Female	20	36.4%
Male	35	63.6%
Total	55	100.0%

There were 20 females (36.4%) and 35 males (63.6 %) in our study.

Table 2: Age group Distribution

Age(years)	Number	Percent
<30	6	10.9%
31 to 40	8	14.5 %
41 to 50	10	18.2 %
51 to 60	9	16.4 %
61 to 70	16	29.1 %
71 to 80	6	10.9 %
Total	55	100.0 %

Majority of the patients in our study belonged to the age group 61 to 70 years (29.1%) followed by 41 to 50 years (18.2%).

Table 3: History of Smoking

Smoking	Number	Percent
No	38	69.1%
Yes	17	30.9%
Total	55	100.0 %

We had 17 Smokers (30.9 %) and 38 Non-smokers (69.1 %).

Table 4: History of TB

History of TB	Number	Percent
No	48	87.3%
Yes	7	12.7 %
Total	55	100.0 %

A history of TB was found in 7 patients (12.7 %). All patients were HIV negative

Table 5: Multiple LN Stations

Multiple LN Stations	Number	Percent
No	45	81.8%
Yes	10	18.2%
Total	55	100.0 %

Majority of the patients had single LN Station, 45 (81.8%) while 10 patients (18.2%) had multiple LN Station.

Table 6: Lymph node station on CT

Lymph node stations	Number	Percent
10L,4R	1	1.8%
10R,4R,7	1	1.8%
10R,10L	1	1.8%
4R,7	1	1.8%
7,10R	1	1.8%
7,10R,4R	1	1.8%
7,10L	1	1.8%
7,4R	1	1.8%
10R,4R	2	3.6%
10R	6	10.9%
4R	6	10.9%
10L	7	12.7%
7	26	47.3%
Total	55	100.0%

*Arranged according to number of cases

Most common lymph node station was 7 ,seen in 26 patients(47.3%) followed by 10L seen in 7 cases (12.7%) and 4R,10R seen in 6 cases each (10.9%).

Table 7: Diagnosis

Diagnosis	Number	Percent
Non small cell cancer	1	1.8%
Poorly differentiated malignancy	1	1.8%
Poorly differentiated small cell Ca	1	1.8%
Adenocarcinoma of lung	5	9.09%
Malignancy(others)	5	9.09%
TB-probable	2	3.6%
TB-confirmed	15	27.3%
Chronic inflammation	3	5.5%
Reactive Lymphadenopathy	16	29.1%
Necrotising granuloma	2	3.6%
Sarcoid and Sarcoid like	3	5.5%
Inadequate sample	1	1.8%
Total	55	100.0%

Most common diagnosis in our study was reactive lymphadenopathy, seen in 16 cases(29.1%) followed by confirmed TB in 15 cases(27.3%),malignancy (OTHERS) in 5 cases(9.09%),sarcoid and sarcoid like in 3 cases(5.5%),chronic inflammation in 3 cases (5.5 %),probable TB in 2 cases (3.6%),necrotising granuloma in 2 cases (3.6%),adenocarcinoma of lung in 5 cases(9.09%),poorly differentiated malignancy and poorly differentiated small cell Ca and non small cell ca in one case each(1.8%).One case had inadequate sample

Table 8: Diagnosis Simplified

Diagnosis	Number	Percent
Inadequate Sample	1	1.8%
Others	8	14.5%
Malignancy	13	23.6%
Reactive Lymphadenopathy	16	29.1%
TB	17	30.9%
Total	55	100.0%

TB was the most common diagnosis in 17 cases (30.9%), followed by reactive Lymphadenopathy in 16 cases(29.1%),malignancy in 13 cases(23.6%).

Table 9: Staging of cancer

Staging of cancer	Number	Percent
3a	2	15.4%
3b	6	46.1%
Adenocarcinoma lung stage 4	5	38.5%
Total	13	100.0%

Out of 13 cases diagnosed with malignancy, 5 cases had adenocarcinoma of lung stage 4 (38.5%), 6 had stage 3b Ca (46.1%), 2 cases had stage 3a Ca (15.4%).

Table 10: Complications

Complications	Number	Percent
Fever	3	5.4%
Hoarseness of voice	1	1.8%
Ventricular premature complex	1	1.8%
Bleeding	21	38.1%
None	29	52.7%
Total	55	100.0%

Total 26 cases had complications (47.3%), out of which the most common was bleeding which was mild in 21 cases (38.1%), fever in 3 cases (5.4%). One case each had hoarseness of voice and ventricular premature complex. 29 cases had no complication (52.7%).

Table 11: Age group and Diagnosis

Diagnosis	≤30 yrs	31 to 40	41 to 50	51 to 60	61 to 70	71 to 80	Total
Inadequate sample	0	1	0	0	0	0	1
Malignancy	0	1	2	3	5	2	13
Others	2	0	2	2	2	0	8
Reactive lymphadenopathy	1	2	2	3	6	2	16
TB	3	4	4	1	3	2	17
Total	6	8	10	9	16	6	55

$\chi^2=17.83, P=0.598$, Not Significant

There was no statistical significance between the different diagnosis and age groups ($p>0.05$). Out of 13 cases of malignancy, 5 were in age group 61 to 70 yrs (38.5%) and 3 were seen in 51 to 60 yrs (23.1%). Out of 17 cases of TB, 4 cases each (23.5%) were from age group 31 to 40 and 41 to 50 years. Out of 16 cases

with reactive Lymphadenopathy, 6 cases were from the age group 61 to 70 years (37.5%) and 3 cases were from age group 51 to 60 years (18.75%).

In general, younger age groups (18-50 years) had more cases of TB as compared to older age group (51 to 80 years) who had malignancy and reactive Lymphadenopathy more common.

Table 12: Gender and Diagnosis

Diagnosis	Female	Male	Total
Inadequate sample	1	0	1
Malignancy	3	10	13
Others	3	5	8
Reactive Lymphadenopathy	6	10	16
TB	7	10	17
Total	20	35	55

$\chi^2=2.92, P=0.57$, Not Significant

Our study observed that amongst 35 males, 10 patients each had malignancy (28.6%), reactive Lymphadenopathy (28.6%) and TB (28.6%). Out of 20 females, 7 had TB (35%) followed by 6 cases who had reactive Lymphadenopathy (30%), 3 cases had malignancies (15%). There was no significant association between gender and diagnosis.

Table 13: Smoking and Diagnosis

Diagnosis	Smoker	Non-Smoker	Total
Inadequate sample	0	1	1
Malignancy	10	3	13
Reactive Lymphadenopathy	5	11	16
TB	0	17	17
Others	2	6	8

Total	17	38	55
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$\chi^2=21.07, p<0.001$, Significant

There was a significant association between history of smoking and diagnosis. Out of 17 cases who had history of smoking, 10 cases had malignancy (58.8%) and 5 had reactive Lymphadenopathy (29.4%). Out of 13 non-smokers, 17 had TB (44.7%) followed by 11 cases who had reactive Lymphadenopathy (28.9%).

Table 14: Number of LN and Diagnosis

Diagnosis	Multiple LN	Single LN	Total
Inadequate sample	0	1	1
Malignancy	5	8	13
Reactive Lymphadenopathy	1	15	16
TB	3	14	17
Others	1	7	8
Total	10	45	55

$\chi^2=4.70, p=0.03$, Significant

Significant association was seen between the presence of malignancy and multiple LN. Out of total 10 cases with multiple LN, 5 had malignancy (50%), while out of 45 cases with single LN involvement, only 8 had malignancy (17.8%). Single LN involvement had 15 cases of reactive lymph nodes (33.3%) and 14 cases had TB (31.1%).

DISCUSSION

Approach to the diagnosis of respiratory diseases usually needs a cumulative study of detailed clinical history, physical examination, laboratory investigations, chest radiograph and HRCT thorax, especially in the diagnosis of mediastinal lymphadenopathy and other peritracheobronchial lesions. It is a challenging task to a respiratory physician to deal with undiagnosed mediastinal lymphadenopathy. EBUS TBNA is superior to conventional TBNA as it gives real time nodal visualisation, accessibility of more stations, having more sensitivity and as valuable tool especially in staging of lung cancer. Murthi et al retrospectively analysed subjects who underwent EBUS-TBNA followed by a confirmatory surgical procedure to evaluate the accuracy of EBUS-TBNA in the diagnosis of mediastinal disease. They found EBUS -TBNA results accurate. (7)

AGE & GENDER

There were 20 females (36.4%) and 35 males (63.6%) in our study. We saw male majority in our study with a male to female ratio of 1.75: 1. Eom JS et al had female majority in their study, with 61% females on their study. [8] Majority of the patients in our study belonged to the age group of 61 to 70 years (29.1%) followed by 41 to 50 years (18.2%). Mean age of the study participants was 52.52±15.96 years. Mean age in the study by Eom JS et al was 47.1 ± 17.1 years, less than our study. [8]

SMOKING

We observed that 17 patients had history of smoking (30.9%), while rest 38 patients were non-smokers (69.1%). N Navani et al reported that out of 120

patients, 42 had history of smoking (35%), similar to our study. [9]

TB, HIV

We observed that 7 patients had history of TB (12.7%) while rest 48 didn't have it (87.3%). All patients were HIV negative (100%). TG Tournoy et al observed that out of all lung lesions, 8% cases had TB and 2.4% had HIV. [10]

MULTIPLE LN STATIONS

Majority of the patients, 45 (81.8%) had single lymph node station while 10 patients (18.2%) had multiple lymph node stations.

Vincent BD et al reported that out of all patients who underwent EBUS TBNA, majority had single lymph node involvement (76%) as compared to multiple lymph nodes (24%). [11]

Most common lymph node station was 7, seen in 26 patients (47.3% followed by 10L seen in 7 cases (12.7%) and 4R, 10R seen in 6 cases each (10.9%).

Takahiro Nakajima et al in 2009 in a similar study reported that the most commonly occurring lymph node station was subcarinal, station 7, seen in 52% cases, similar to our study. [12]

SAMPLE ADEQUACY

54 cases had adequate sample (98.2%) while in only 1 case (1.8%) it was inadequate. So one can get a good quantity of sample for investigations.

GRANULOMATOUS ETIOLOGY

Out of all cases, 22 had granulomatous etiology (40%), which had 19 cases of TB (34.5%) and 3 cases of sarcoidosis (5.5%). Valliappan M et al in 2019 studied patients undergoing EBUS-TBNA and found that Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) is currently the preferred initial modality for evaluating intrathoracic lymphadenopathy. They found that most common causes for granulomatous etiology were TB & Sarcoidosis, similar to our study findings. [13]

Takahiro Nakajima et al in their study of EBUS-TBNA revealed non-caseating granulomas or epithelioid cells in 32 of 35 cases (91.4%). Which was higher than our study. [12]

FINAL REPORT

Most common diagnosis in our study was reactive lymphadenopathy seen in 16 cases (29.1%) followed by confirmed TB in 15 cases (27.3%), malignancy in 8 cases (14.5%), Sarcoid and Sarcoid like in 3 cases (5.5%), chronic inflammation in 3 cases (5.5%), probable TB in 2 cases (3.6%), adenocarcinoma of lung in 2 cases (3.6%), necrotizing granuloma in 2 cases (3.6%), poorly differentiated malignancy and poorly differentiated small cell Ca and non-small cell Ca in one case each (1.8%). One case had inadequate sample (1.8%).

TB was the most common diagnosis in 17 cases (30.9%), followed by reactive Lymphadenopathy in 16 cases (29.1%), malignancy in 13 cases (23.6%) and others as described above in 8 cases (14.5%). Thus EBUS TBNA in our study was helpful in diagnosing TB & CA of lung.

Yang li Lu et al studied 201 patients who underwent EBUS-TBNA and found that EBUS- TBNA is very helpful in diagnosing carcinoma of lung and TB effectively. This study indicates that EBUS-TBNA provides high diagnostic sensitivity and specificity for TB lymphadenitis and sarcoidosis (72.4% vs. 71.4% and 100.0% vs. 10.00%, respectively). [5]

Juliana Guarize et al in 2018 studied EBUS-TBNA for diagnostic efficiency. They divided patients in to five different groups 1: lung cancer staging, 2: pathological diagnosis in advanced stage lung cancer, 3: lymphadenopathy in previous malignancies, 4: pulmonary lesions, and 5: unknown origin lymphadenopathy. They concluded that EBUS-TBNA is useful and accurate in a high percentage of cases who needs modern oncological therapy, guiding the best treatment options in lung cancer and avoiding the invasive procedures in benign disease. [14]

STAGING OF CANCER

Out of 13 cases diagnosed with malignancy, 5 cases had adenocarcinoma of lung stage 4 (38.5%), 6 had stage 3b (46.1%), 2 cases had stage 3a (15.4%). G S Bindert et al reported that EBUS TBNA is important for higher RNA yield for multiple biomarker testing in lung carcinoma. They suggested EBUS TBNA for better staging of cancer. [15] Gu P et al conducted a study on use of EBUS TBNA for staging of lung cancer & found it useful as compared to other methods. [16]

COMPLICATIONS

Total 26 cases had complications (47.3%), out of which most common was minor bleeding in 17 cases (30.9%), followed by bleeding in 4 cases (7.3%), post procedure fever in 2 cases (3.6%). One case each had fever, hoarseness of voice and ventricular premature complex (1.8% each).

Chen C et al reported very few major complications (5.2%) seen as bleeding in 3.1% and fever, hoarseness of voice in 2.1% cases. [17] Holty JC et al reported that

TBNA is safe with few complications. The pooled severe complication rate was 0.3%. [18]

AGE GROUPS & DIAGNOSIS

There was no statistical significance between the different diagnosis and age groups ($p > 0.05$). Out of 13 malignancies, 5 were seen in age group of 61 to 70 years (38.5%) and 3 were seen in 51 to 60 years (23.1%). Out of 17 cases of TB, 4 cases each (23.5%) were from age group of 31 to 40 and 41 to 50 years. Out of 16 cases with reactive Lymphadenopathy, 6 cases were from the age group of 61 to 70 years (37.5%) and 3 cases were from age group of 51 to 60 years (18.75%).

In general, younger age groups (18 to 50 years) had more cases of TB as compared to older age people (51 to 80 years) who had malignancy and reactive Lymphadenopathy more common.

Erer OF et al reported that lung cancer was associated with older age groups (61 to 80 years) as compared to younger patients. [19]

GENDER & DIAGNOSIS

Our study observed that amongst 35 males, 10 patients each had malignancy (28.6%), reactive Lymphadenopathy (28.6%) and TB (28.6%). Out of 20 females, 7 had TB (35%) followed by 6 cases who had reactive Lymphadenopathy (30%), 3 cases had malignancies (15%). There was no any significant association between the gender and diagnosis ($p = 0.57$).

Park SK et al found that males had more cases with lung cancer (32%) as compared to females, (21%) and females had more cases of TB (38%) as compared to males (29%). [20]

SMOKING & DIAGNOSIS

There was significant association between the history of smoking and diagnosis ($p < 0.001$). Out of 17 cases who had history of smoking, 10 cases had malignancy (58.8%) and 5 had reactive Lymphadenopathy (29.4%). Out of 38 cases without history of smoking, 17 had TB (44.7%), followed by 11 cases who had reactive Lymphadenopathy (28.9%).

Numerous studies [21-23] have reported positive correlation of smoking and lung cancer. Gritz ER et al reported majority of the patients who had smoking reported lung cancer (685) as compared to those without smoking (24%). [23]

MULTIPLE LN & DIAGNOSIS

Significant association was seen between the presence of malignancy and multiple lymph nodes ($p = 0.03$). Out of total 10 cases with multiple lymph nodes, 5 had malignancies (50%) while out of 45 cases with single lymph node involvement, only 8 had malignancies (17.8%). Single lymph node involvement had 15 cases of reactive lymph nodes (33.3%) and 14 cases had TB (31.1%)

Folch E et al reported that of all cases reported for EBUS to detect CA lung, majority had multiple lymph nodes (72%) showing strong correlation between the multiple lymph nodes and lung CA. [24]
CA lung should be suspected in cases with multiple lymph nodes.

DIAGNOSIS & COMPLICATIONS

No significant association was seen between the diagnosis and complications ($p=0.449$). Total 26 cases had complications (47.3%) and 29 had no complications (52.7%).

Out of 4 cases which had bleeding, 2 had TB (50%) and each had malignancy & reactive Lymphadenopathy (25%).

One patient with TB had hoarseness of voice.

Total 17 cases had minor bleeding, commonly in 6 cases of malignancy (35.3%) and 4 cases each of reactive Lymphadenopathy & TB (23.5%).

Dhooria S et al reported that out of the total 1005 EBUS-TBNA performed during their study period, the complications related to EBUS were observed in 39% subjects. Majority of them were minor and self-limiting; major complications occurred in 11 (1.1%) subjects and included respiratory failure requiring assisted ventilation ($n=6$), arrhythmia ($n=3$), and hypotension ($n=2$). Escalation of the level of care was needed in only 8 (0.8%) subjects. [25]

Eapen GA et al also reported minor complications were seen in 24.2% cases and some major complications were seen in very few cases. Pneumothorax occurred in seven patients (0.53%) and escalations in level of care occurred in 14 patients (1.06%).(26)

CONCLUSION

EBUS-TBNA is a useful test for diagnosing mediastinal and hilar lymphadenopathy. Moreover, this technique can prevent further invasive evaluation in patients whose histological and microbiological tests are non-diagnostic. EBUS-guided fine needle aspiration is not only a safe procedure but also helps us getting tissue diagnosis with minimal invasion. EBUS-TBNA can be used as a diagnostic option for pulmonary TB, CA Lung, Sarcoidosis etc., although additional experience is required before it is used in general practice.

LIMITATIONS

- Our study was conducted in one tertiary care hospital of Pune and so, data cannot predict the overall situation in the country.
- In EBUS-TBNA all lymph nodes stations are not accessible.
- Steep Learning Curve
- Must need expertise
- Our study contained results with major percentage of cases being malignancy and tuberculosis, which reflects our specific recruitment of such group of patients.

- We did not compare the results by a gold standard method like surgery. However, similar studies usually had the same limitation
- Since prevalence of tuberculosis is high, the results are altered, i.e. diagnosis of tuberculosis is more which may not be the case in western countries where malignancies are diagnosed. So, there may be bias in the results of current studied group.

RECOMMENDATIONS

- EBUS-TBNA is an important tool in staging of lung cancer.
- EBUS is a great armamentarium to the pulmonologist, as it is real time technique.
- It is also useful in the diagnosis of isolated mediastinal TB lymphadenopathy, sarcoidosis.
- Practicing pulmonologists, pulmonary medicine residents- future pulmonologists need adequate and continuous learning to expertise in EBUS-TBNA technique.

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