Role of EBUS-TBNA in Mediastinal Staging of NSCLC Patients

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Abstract

Purpose Mediastinal staging in non-small-cell lung carcinoma (NSCLC) is essential for appropriate treatment. Invasive mediastinal staging is necessary and mediastinoscopy has been the gold standard, but it is associated with morbidity. The aim of this study is to evaluate the efficacy of endobronchial ultrasonography transbronchial needle aspiration (EBUS-TBNA), compare it with mediastinoscopy, and assess the endosonographic features of lymph nodes for prediction of metastasis.

Methods This is a retrospective study of 200 patients with NSCLC who underwent EBUS-TBNA from January 2017 to December 2019. The patients with potentially resectable NSCLC who underwent EBUS-TBNA were included. Standard definitions of sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and diagnostic accuracy were used to determine the diagnostic performance of EBUS-TBNA.

Results A total of 200 patients and 616 nodes were studied, out of which 515 were benign and 101 were malignant. Out of 200 cases, 129 (64.5%) had <N2 disease, 59 (29.5%) had N2 disease, and 12 (6%) had N3 disease. EBUS-TBNA had a sensitivity of 78.87%, specificity of 96.12%, NPV of 89.2%, PPV of 91.8%, and accuracy of 90%. Ultrasonography (USG) features of 297 nodes were available and statistical significance was seen in rounded shape, size greater than 10 mm, ill-defined nodal margins, absence of hilum, and hypoechoic echotexture ($p < 0.05$).

Conclusion EBUS-TBNA is a safe and efficacious procedure for mediastinal sampling of NSCLC patients. Familiarity with endosonographic features of lymph nodes, which can predict malignancy in nodes, may further improve the yield of EBUS-TBNA and reduce under-staging.

Keywords
- endobronchial ultrasound
- FNA
- non-small-cell lung cancer

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Table 1 Patient selection criteria

Inclusion criteria	Exclusion criteria
● EBUS-TBNA performed in patients with biopsy-proven, potentially resectable NSCLC ● No distant metastases as confirmed with whole-body PET-CT and brain MRI	● Images not available on PACS ● No histopathological or USG records available

Abbreviations: EBUS-TBNA, endobronchial ultrasonography transbronchial needle aspiration; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung carcinoma; PACS, picture archiving and communication systems; PET-CT, positron emission tomography and computed tomography; USG, ultrasonography.

Introduction

Precise mediastinal staging of non-small-cell lung carcinoma (NSCLC) is important for guiding treatment and accurate prognostication. In the absence of distant metastases (M0) or involvement of mediastinal lymph nodes (N0), patients are considered potential candidates for surgical resection.[1] Noninvasive modalities, like contrast-enhanced computed tomography (CECT) or positron emission tomography and computed tomography (PET-CT), are used in imaging mediastinal lymphadenopathy. However, patients with a radiologically normal mediastinum may have occult nodal metastases, and such cases may be as high as 35%.[2] On computed tomography (CT), significant lymphadenopathy is defined as lymph nodes with a short axis diameter of 1 cm or more. However, smaller lymph nodes can have metastatic foci, while large nodes may be benign. PET-CT has superior sensitivity, specificity, and high negative predictive value (NPV) for normal-sized and enlarged lymph nodes.[3] However, a Cochrane meta-analysis assessing the diagnostic accuracy of PET-CT for N2 mediastinal nodes concluded that PET-CT alone was insufficient for treatment decisions.[4] For high accuracy, invasive mediastinal staging is required in potentially resectable cases.[5] It is performed using methods like mediastinoscopy, open surgery, video-assisted thoracoscopic surgery (VATS), and endobronchial ultrasonography transbronchial needle aspiration (EBUS-TBNA). While mediastinoscopy is considered the gold standard, it is associated with minor (3.2%) and major (3.5%) complications and sporadic mortality ($<1\%$)[5] and complications such as bleeding and recurrent nerve paralysis.[6] The current Dutch and European guidelines recommend mediastinal staging by EBUS and/or endoscopic ultrasound (EUS).[1]

This retrospective study compares the diagnostic yield of EBUS/EUS with mediastinoscopy/final histopathology/cytology and reviews the endosonographic features recorded during mediastinal staging.

Materials and Methods

After obtaining permission from the institutional review board and the ethics committee, a retrospective study of data of patients with NSCLC who underwent EBUS-TBNA from January 2017 to December 2019 was carried out. Data were collected from the hospital's electronic medical records (EMR) and picture archiving and communication systems (PACS). The inclusion and exclusion criteria for the study are in shown in ►**Table 1**.

Procedure

All EBUS-TBNA procedures were performed in our institute under total intravenous anesthesia (TIVA), by a team of thoracic anesthetists, thoracic surgeons, chest physicians, and interventional radiologists. EBUS-TBNA was performed with an echo bronchoscope (Pentax EB-1970UK, Pentax Medical and Hitachi Medical Systems). The nodal stations were assessed and screened with ultrasonography (USG)/color Doppler and sampled as per the Mountain–Dresler map,[7,8] starting with contralateral hilar nodes (stations 10 and 11), followed by right and left lower paratracheal nodes (stations 4R and 4L), subcarinal node (station 7), right and left upper paratracheal nodes (stations 2R and 2L), and paraesophageal node (station 8). On USG, nodes with a short-axis diameter (SAD) of more than 3 mm were identified for sampling with care taken to avoid injury to blood vessels and vital mediastinal structures (►**Fig. 1**). The ipsilateral hilar nodes were not sampled. Sampling was done using a 22-gauge EBUS-TBNA needle (Echotip, Cook medical) under direct ultrasound guidance (►**Fig. 2**). When required, a 22-gauge needle with a provision for obtaining cores with aspirate was used (Echotip Procore, Cook Medical). The exact sampling steps are detailed in ►**Fig. 3**.

In selected cases, two preparations (slides and cell block) were used for evaluating the specimens. In the cases where the on-site cytologist reported atypical cells in contralateral hilar nodes (N3 disease), further sampling was abandoned.

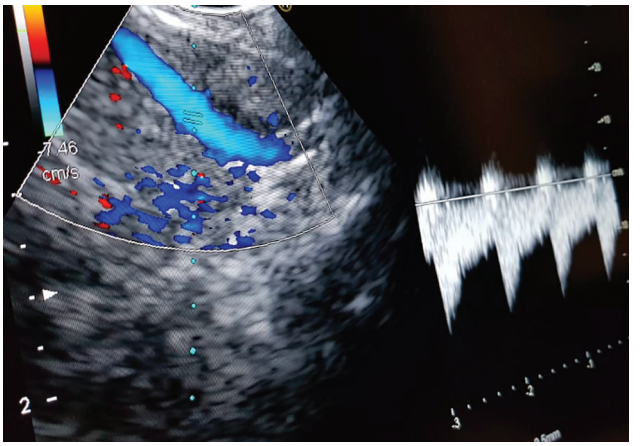

Fig. 1 Endobronchial ultrasound (EBUS) with Doppler and spectral waveform showing vessel in close proximity to the mediastinal node.

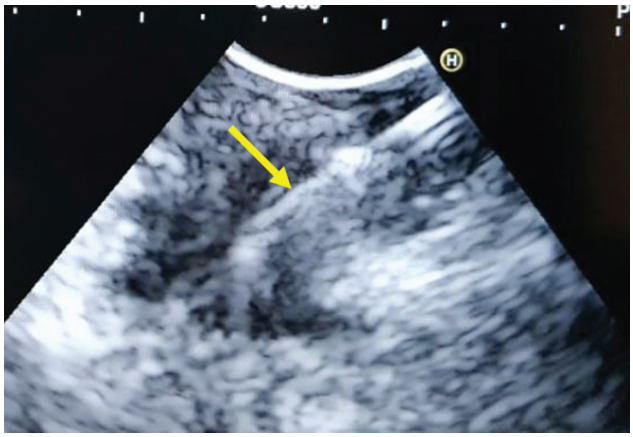

Fig. 2 Real-time endobronchial ultrasound (EBUS) guided lymph node sampling showing needle tip within the lymph node (*arrow*).

An independent pathologist further confirmed the on-site diagnosis in all cases. ►**Fig. 4** shows further patient management after EBUS.

Definitions

The definitions used to determine the diagnostic performance are the following:

- *Positive EBUS-TBNA:* Adequate aspirates with atypical/malignant cells.
- *Negative EBUS-TBNA:* Adequate aspirates without malignant cells.
- *True positive and negative results:* For those patients in whom further mediastinoscopy/surgical staging or resection was done, lymph nodes with atypical/malignant cells on the final histopathological report (HPR) were considered true positive and those without were considered true negative. For patients who did not undergo further staging by mediastinoscopy or surgery, EBUS-TBNA slides reported by an independent pathologist as having atypical cells were considered true positive and those with a negative report were considered true negative.
- *Sensitivity:* true positive ÷ (true positive + false negative).
- *Specificity:* true negative ÷ (true negative + false positive).
- *NPV:* true negative ÷ (true negative + false negative).
- *Diagnostic accuracy:* (true positive + true negative) ÷ (true positive + false positive + true negative + false negative).

Statistical Analysis

Standard definitions of sensitivity, specificity, NPV, positive predictive value (PPV), and diagnostic accuracy were used to determine the diagnostic performance of EBUS-TBNA. Chi-squared test and Fischer's exact test were used to examine the association of two or more categorical variables (such as an association of size or presence of hilum with final HPR/cytology report). A *p*-value less than 0.05 was considered statistically significant (5% level of significance). The statistical analyses were done using IBM SPSS statistical software version 24.

Results

A total of 200 patients had undergone EBUS-TBNA from January 2017 to December 2019. Out of these, 39 were

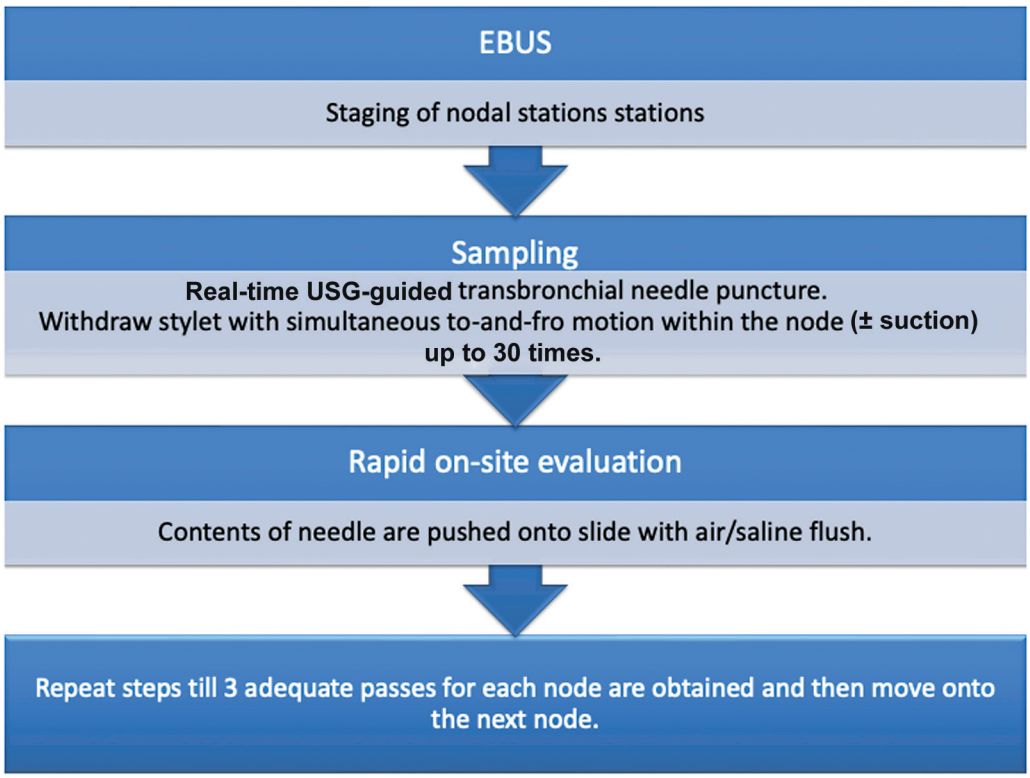

Fig. 3 Flowchart depicting steps of endobronchial ultrasonography transbronchial needle aspiration (EBUS-TBNA).

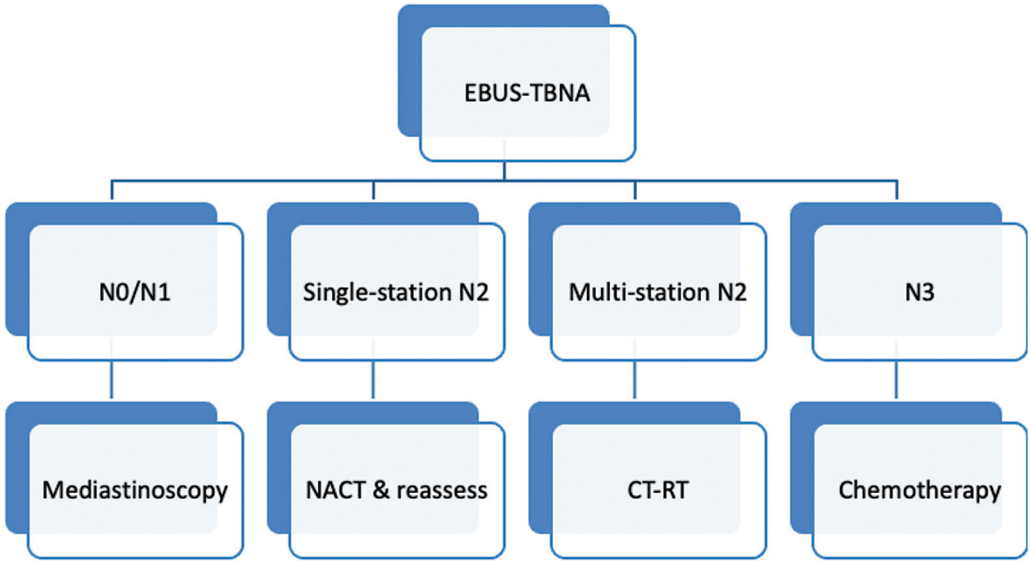

Fig. 4 Flowchart depicting further management after endobronchial ultrasonography transbronchial needle aspiration (EBUS-TBNA). CT-RT, Chemotherapy and radiation therapy; CT-RT, Chemotherapy and radiation therapy.

Table 2 Frequency of stations sampled and station-wise distribution of malignant nodes

Station	Benign	Malignant	Total
7	147 (76.5%)	45 (23.4%)	192 (31.2%)
4R	132 (84.1%)	25 (15.9%)	157 (25.5%)
4L	112 (84.8%)	20 (15.1%)	132 (21.5%)
11L	51 (96.2%)	2 (3.7%)	53 (8.6%)
2L	15 (79%)	4 (21%)	19 (3.08%)
2R, 11R, 10R, 10L, 12R, 12L	58 (92.1%)	5 (7.9%)	63 (10.2%)

females and 161 were males. The median age of the patients was 59 years (range: 23–78 years).

Nodes/Stations Sampled and Station-Wise Distribution of Malignancy

Total of 616 nodes were sampled in 200 patients. ►**Table 2** shows the frequency of stations sampled and the station-wise distribution of malignancy. Station 7 had the highest number of malignant nodes (23.4%), while station 11L had the least (~3.7%).

Diagnostic Yield

Out of 200 cases, 115 underwent surgical mediastinal sampling (SMS). Of the 616 nodes, 515 were benign and 101 were malignant.

Of the 200 cases, 15 cases were falsely negative on EBUS-TBNA and under-staged as <N2 (N0/N1). Out of these, 13 cases were re-staged as N2 and 2 cases as N3 disease after mediastinoscopy. One case staged as N2 on EBUS was found to be multistation N2 on the final HPR of the resected specimen (►**Fig. 5**). In five cases, nodes labeled as malignant on EBUS turned out to be benign on mediastinoscopy or independent cytologist review. In five cases, nodes labeled as malignant on EBUS turned out to be benign on mediastinoscopy (►**Fig. 6**) or independent cytologist review.

The location of nodes recorded at the time of EBUS and SMS helped in mediastinal staging of patients and retrospective analysis of these reports and the histopathology reports of the resected nodes showed that 129/200 cases (64.5%) had <N2 disease, 59 (29.5%) had N2 disease, and 12 (6%) had N3 disease (►**Fig. 7**). Comparing this to EBUS-TBNA results, 56 were true positives on EBUS; 124 were true negatives, 15 were false negatives, and 5 were false positives. ►**Table 3** details the diagnostic yield.

Of the 200 cases, USG characteristics of 108 cases (297 lymph nodes) were available. The features assessed included the following: lymph node size (short axis ≤10 or >10 mm); echo pattern (normal, hypoechoic, heterogenous); presence or absence of hilum; shape (oblong or round; ►**Figs. 8** and **9**); presence or absence of necrosis and calcification; and margins (well-defined or ill-defined). ►**Table 4** details the correlation of USG features with the presence of malignancy.

Correlation of Lymph Node Size with Malignancy

Out of 297 lymph nodes assessed, 115 had an SAD greater than 10 mm; of these, 75.7% ($n = 87$) were benign and 24.3% ($n = 28$) were malignant. In 182 nodes, the SAD was less than 10 mm; of these, 11.5% ($n = 21$) had malignant cells and 88.5% ($n = 161$) were benign. The chi-square test revealed a p-value of 0.004, which suggests a significant correlation

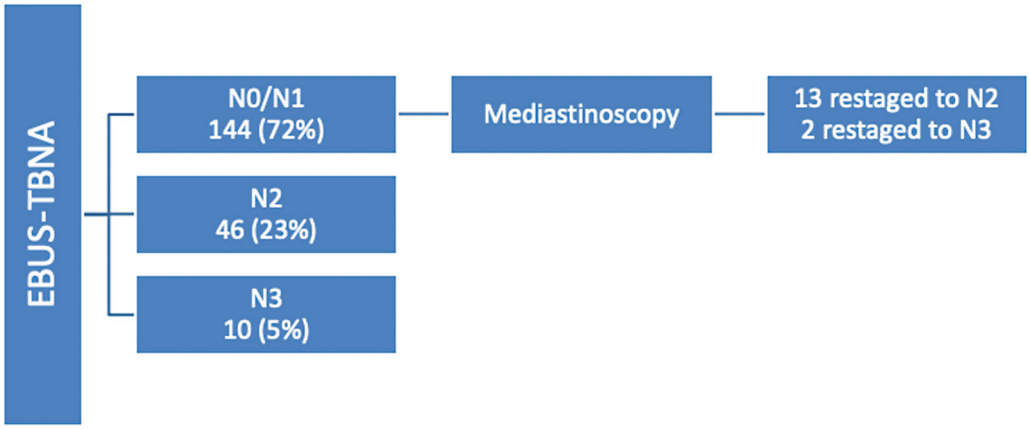

Fig. 5 Mediastinal staging of non-small-cell lung carcinoma (NSCLC) patients after endobronchial ultrasound (EBUS) and mediastinoscopy. EBUS-TBNA, endobronchial ultrasonography transbronchial needle aspiration.

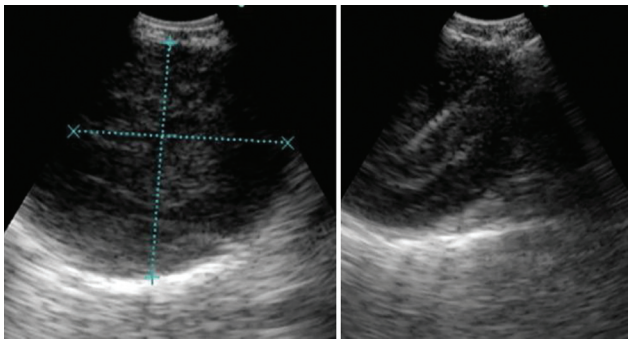

Fig. 6 Enlarged, hypoechoic lymph node showing necrotizing granulomas after surgical mediastinal sampling.

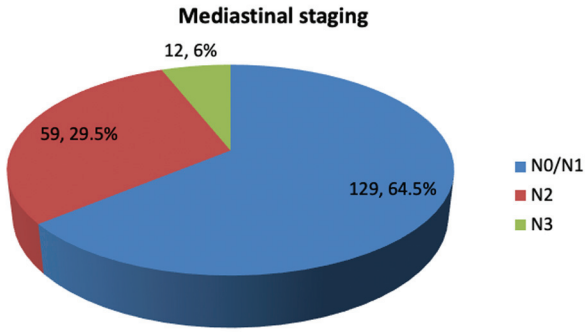

Fig. 7 Stage-wise distribution of patients as per the final histopathological report (HPR)/cytology.

between the node size (SAD > 10 mm) and the presence of malignancy in the node.

Correlation of Lymph Node Shape with Malignancy

Out of 297 lymph nodes, 255 were oblong in shape, of which 9.8% ($n = 25$) were malignant, while 90.2% ($n = 230$) were benign. Forty-two lymph nodes had a rounded shape (defined as a long axis-to-short axis ratio of <1.5), of which 57.1% ($n = 24$) were malignant and 42.9% ($n = 18$) were benign. The chi-squared test showed a p-value of less than 0.001, which suggests a significant correlation between the round shape of a lymph node and its malignant nature.

Correlation of Lymph Node Hilum with Malignancy

Out of 297 lymph nodes, 243 had a preserved nodal hilum, of which 7% ($n = 17$) were malignant and 93% ($n = 226$) were benign. Fifty-four nodes had an indistinct or absent hila, of which 59.3% ($n = 32$) were malignant and 40.7% ($n = 22$) were benign. The chi-squared test revealed a p-value of less than 0.001.

Correlation of Lymph Node Echotexture with Malignancy

Of 297 lymph nodes, 249 had a normal echotexture, of which 92.4% ($n = 230$) nodes were benign and 7.6% ($n = 19$) were malignant. Forty-three nodes had hypoechoic areas; of these, 65.1% ($n = 28$) of the nodes were malignant and 34.9% ($n = 15$) nodes were benign. Only five nodes had a heterogeneous echotexture, of which 40% ($n = 2$) nodes were malignant and 60% ($n = 3$) were benign. Fischer's exact t-test was applied and the p-value was found to be less than 0.001.

Table 3 Staging comparison: endobronchial ultrasonography (EBUS) versus final histology/cytology

EBUS vs. mediastinoscopy		Mediastinoscopy or final cytology		
		Positive	Negative	Total
EBUS	Positive	56	5	62
	Negative	15	124	138
	Total	71	129	200

Correlation of Lymph Node Characteristics with the Presence of Granulomas

Tuberculosis and other granulomatous diseases have a widespread prevalence in India. Ten patients showed the presence of granuloma in their mediastinal nodes. Out of these, six had normal-appearing nodes, three cases had necrotic nodes, and one patient had hypoechoic nodes. Statistical analysis revealed a p-value of 0.069. Five patients had mediastinal

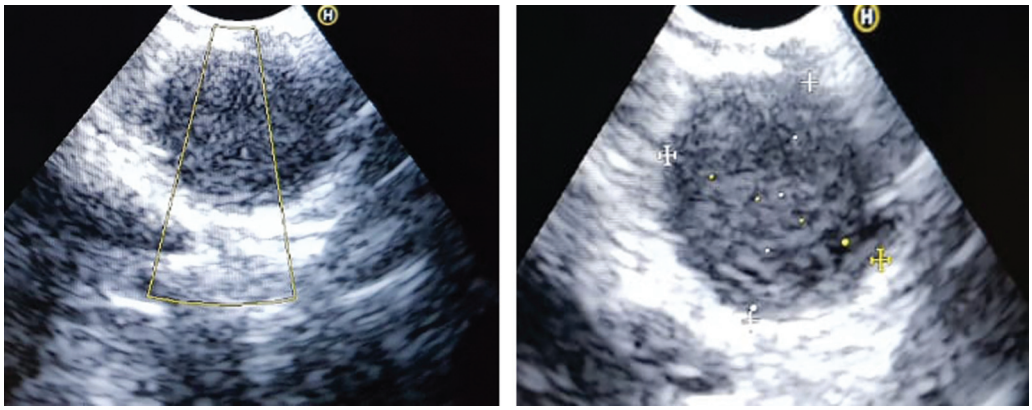

Fig. 8 Endobronchial ultrasound (EBUS) showing an example of a mediastinal node with features predictive of malignancy: rounded shape, absence of well-defined vascular hilum, and heterogeneous/hypoechoic echotexture.

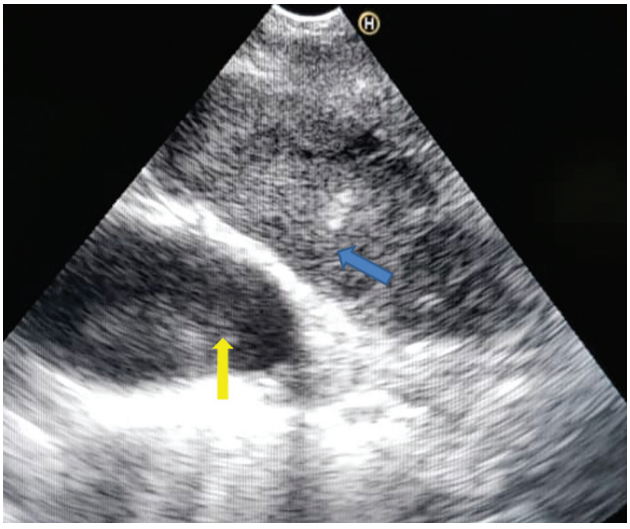

Fig. 9 Enlarged, hypoechoic lymph node showing necrotizing granulomas after surgical mediastinal sampling.

nodes positive for malignancy and concurrent granulomatous adenitis.

Correlation of Nodal Necrosis and Malignancy

Out of the 297 lymph nodes, 288 did not show necrosis; of these, 84.3% ($n = 243$) were benign and 15.6% ($n = 45$) were malignant. Only nine nodes showed necrosis and out of these 55.6% ($n = 5$) were benign and 44.4% ($n = 4$) were malignant. Statistical analysis showed a p-value of 0.044.

Correlation of Nodal Calcification and Malignancy

Out of the 297 nodes, 279 did not show calcification; out of these, 83.5% ($n = 233$) were benign and 16.5% ($n = 46$) nodes were malignant. Eighteen nodes showed calcification and of these, 16.7% ($n = 3$) were malignant and 83.3% ($n = 15$) were benign. Statistical analysis showed a p-value of 0.2.

Correlation of Lymph Node Margins and Malignancy

Out of the 297 nodes, 285 had well-defined margins, of which 85.6% ($n = 244$) were benign and 14.4% ($n = 41$) were malignant. Twelve nodes had ill-defined margins, of which 33.3% ($n = 4$) were benign and 66.7% ($n = 8$) were malignant. Statistical analysis showed a p-value of less than 0.001.

Complications

No major complications were seen in any of the cases.

Discussion

Data analysis showed that our EBUS-TBNA technique had 96.12% specificity, 91.8% PPV, 78.8% sensitivity, 89.2% NPV, and overall accuracy of 90%. The results of our study are within the range of EBUS-TBNA sensitivity (52–92%), NPV (57–93%), and accuracy (84–96%), as reported in a recent systematic review and meta-analysis by Dhooria et al.[9] Similar results have been reported by Herth et al, who have shown that sensitivity, specificity, and NPV of EBUS-TBNA for detecting malignancy were 89%, 100%, and 98.9%, respectively, in lung cancer patients.[10] Fernández-Bussy et al reported that, in their study, EBUS-TBNA showed a sensitivity of 91.17%, a specificity of 100%, and an NPV of 92.9%.[11] Yasufuku et al conducted a prospective study of 153 patients to compare the diagnostic performance of EBUS-TBNA with mediastinoscopy for staging in NSCLC patients.[12] They found that the sensitivity, NPV, and diagnostic accuracy for mediastinal lymph node staging using EBUS-TBNA were 81%, 91%, 93% and the sensitivity, NPV, and diagnostic accuracy for mediastinal lymph node staging using mediastinoscopy were 79%, 90%, 93%, respectively. There was excellent agreement (91% Kappa index) between EBUS and mediastinoscopy, and the authors concluded that there were no significant differences between EBUS-TBNA and mediastinoscopy for determining the true pathological mediastinal lymph node stage in patients with NSCLC.

Ahuja and Ying reported that sonography is a useful imaging tool in the evaluation of cervical lymph nodes in patients with malignancies of the head, neck, and thorax. For evaluation of mediastinal and hilar lymph nodes, EUS was first accepted as a diagnostic modality in the 1990s.[13] In both cervical ultrasonography and EUS, the morphologic characters of pathologic lymph nodes are well known, and an SAD greater than 10 mm, round shape, indistinct margins, heterogeneous echo pattern, absence of central echogenic

Table 4 Correlation of various ultrasonography (USG) features with malignancy

Correlation of USG features (size, shape, echotexture, presence of hilum, necrosis, and margins with malignancy			Malignant or benign		Total	*p*-value
			Malignant	Benign		
Short axis diameter (size)	≤10 mm	*N*	21	161	182	0.004
		Percentage	11.50	88.50	100.00	
	>10 mm	*N*	28	87	115	
		Percentage	24.30	75.70	100.00	
Shape of lymph node	Oblong	*N*	25	230	255	<0.001
		percentage	9.80	90.20	100.00	
	Rounded	*N*	24	18	42	
		Percentage	57.10	42.90	100.00	
Echotexture	Normal	*N*	19	230	249	<0.001
		Percentage	7.60	92.40	100.00	
	Hypoechoic	*N*	28	15	43	
		Percentage	65.10	34.90	100.00	
	Heterogenous	*N*	2	3	5	
		Percentage	40.00	60.00	100.00	
Lymph node necrosis	No necrosis	*N*	45	243	288	0.044
		Percentage	15.60	84.40	100.00	
	Necrosis present	*N*	4	5	9	
		Percentage	44.40	55.60	100.00	
Lymph node calcification	No calcification	*N*	46	233	279	0.2
		Percentage	16.50	83.50	100.00	
	Calcification present	*N*	3	15	18	
		Percentage	16.70	83.30	100.00	
Lymph node margins	Well defined	*N*	41	244	285	<0.001
		Percentage	14.40	85.60	100.00	
	Ill defined	*N*	8	4	12	
		Percentage	66.70	33.30	100.00	

hilum, and necrosis are considered signs of lymph node metastasis (►**Fig. 7**).[14]

We studied seven endosonographic features of mediastinal nodes: size (>10/< 10 mm), shape (rounded/oblong), presence/absence of hilum, echogenicity (normal/hypoechoic/heterogenous), necrosis, presence of calcification, and nodal margins. Then we correlated these features with the final histopathology/cytology reports. The results of our study suggest that round shape, SAD greater than 10 mm, absent hilum, ill-defined nodal margins, presence of necrosis, and hypoechoic echotexture independently correlate with malignancy ($p < 0.001$). This is consistent with data published by Ahuja and Ying.[13] The presence of foci of calcification (►**Fig. 8**) did not show a correlation with the presence of malignancy ($p = 0.2$) and can be considered a predictor of benignity (significant correlation seen between calcification and granulomas). Fujiwara et al in their study of 487 patients showed that the accuracy in predicting metastasis was 76.4% for size, 79.3% for shape, 65.7% for margin, 89.9% for echogenicity, 63.8% for a central hilar sign, and 86.0% for coagulation necrosis sign. In their study, the *p*-value for size as a predictor of malignancy was not significant, while the values for shape, echogenicity, and the presence of necrosis were highly significant. Also, in their study, the presence/absence of the hilum was not a significant predictor of malignancy ($p = 0.278$), while in our study, the absence of the hilum was a statistically significant predictor of malignancy ($p < 0.001$).[15] Gogia et al, in their study of 402 patients, found that size greater than 11.5 mm was an independent predictor of malignancy ($p < 0.002$) and an oblong/triangular shape (not rounded) was a significant predictor of benign etiology, as was the presence of a central (hilar) vessel ($p < 0.001$).[16] In a study by Gill et al, the EUS features in lung cancer–associated mediastinal lymph nodes were, size greater than 8.3 mm, round shape, and sharp margins, with the predicted probability of 63% when all three were present.[17] ►**Table 5** summarizes the comparative *p*-values of various EBUS features of our study with those of previous studies.

Our study has a few limitations, most important of which is its retrospective nature. The results must be interpreted with caution as the data are from a single, tertiary care center

Table 5 Correlation of various ultrasonography (USG) features with malignancy

USG feature	*p*-value (current study)	*p*-value (Fujiwara et al[15])	*p*-value (Gogia et al[16])
Size (≤10 or >10 mm)	0.044	0.171	<0.002
Shape	<0.001	<0.0001	<0.001
Hilum	<0.001	0.278	<0.001
Echogenicity	<0.001	0.0176	–
Necrosis	<0.001	<0.0001	–
Margins	<0.001	–	–

that specializes in cancer care. All the EBUS-TBNA cases were performed under deep sedation and this increases the diagnostic yield of EBUS-TBNA, as does the presence of on-site cytological evaluation.[18] These resources are not widely available and hence the results may not be generalizable.

Conclusion

EBUS-TBNA is a safe and minimally invasive alternative for mediastinal staging in certain subsets of NSCLC patients and can potentially avoid the more invasive mediastinoscopy in patients with N2 and N3 disease. This is possible because of its high PPV and the high specificity for malignant nodes. However, in patients with <N2 disease on EBUS-TBNA, further staging by mediastinoscopy may be required to avoid unnecessary thoracotomy. EBUS-TBNA also has the unique ability of real-time image-guided sampling, where certain USG characteristics guide the operator to target suspicious nodes to maximize the diagnostic yield and minimize complications.

Ethical Approval
The study was performed after approval from the Institutional Ethics Committee (IEC).

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Conflict of Interest
None declared.

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