The Utility of the Ultrasonographic Characteristics in Differentiating Between Malignant and Tuberculous Mediastinal Lymphadenopathy During EBUS-TBNA

Karan Madan, MD, DM, Manu Madan, MD, DM,* Saurabh Mittal, MD, DM,* Pavan Tiwari, MD, DM,* Vijay Hadda, MD,* Anant Mohan, MD, PhD,* Ravindra M. Pandey, MD,*† and Randeep Guleria, MD, DM**

Background: **Ultrasonographic characteristics may help differentiate between benign and malignant lymph nodes during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). There is limited data on the utility of various ultrasonographic lymph node features to differentiate between malignant and tuberculous mediastinal lymphadenopathy.**

Methods: **We studied the various EBUS ultrasonographic lymph node characteristics (size, shape, margins, heterogeneous echotexture, calcification, central hilar structure, lymph node conglomeration, central intranodal vessel, and coagulation necrosis sign) from our available EBUS-TBNA database.**

Results: **We extracted 1086 subjects [547 with tuberculosis (TB) and 539 with malignant diagnosis]. Comparing the 2 groups (multivariate analysis), presence of central hilar structure (8.2% vs. 2.6%), coagulation necrosis sign (37.5% vs. 13.7%), lymph node conglomeration (30.5% vs. 7.2%), calcification (5.1% vs. 1.5%), and distinct margins (83.5% vs. 69.8%), were significantly more common in TB ($P < 0.05$). On the other hand, malignant lymph nodes were larger and more likely to show the presence of a central intranodal vessel (20% vs. 15.8%, $P = 0.04$, multivariate analysis). The absence of lymph node conglomeration had the highest overall diagnostic accuracy (0.61) for the differentiation between malignant and tuberculous lymph nodes.**

Conclusion: **Sonographic lymph node characteristics may help differentiate malignant and tuberculous mediastinal lymphadenopathy. Contrary to previously published literature, we observed coagulation necrosis sign, heterogeneous echotexture and absent central intranodal vessel, more commonly in TB than malignant nodes. These findings from a TB endemic setting are different from other settings, where the prevalence of lung cancer is high in patients undergoing EBUS-TBNA.**

Key Words: EBUS, ultrasound, mediastinum, lymph node, tuberculosis, lung cancer

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Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a firmly established, minimally invasive modality to sample mediastinal lymph nodes in adults and children.[1–3] The procedure involves using a dedicated bronchoscope with an ultrasound transducer at its distal end. The ultrasonographic assembly allows imaging of the mediastinal lymph nodes while allowing real-time guided aspiration. Various studies have described the utility of the ultrasonographic lymph node characteristics studied during EBUS-TBNA as predictors of the underlying etiology. Most of the previously published literature has focused on the differentiation between benign and malignant mediastinal lymphadenopathy. Few studies have focused on the differentiation between sarcoidosis and tuberculosis (TB) based on the sonographic features.

In the preliminary work about ultrasonographic lymph node characteristics, Fujiwara et al[4] found round shape, distinct margins, heterogeneous echotexture, and presence of coagulation necrosis sign as independent predictors of malignant lymph nodes. A systematic review found the absence of central hilar structure and heterogeneous echotexture associated with malignancy.[5] In a recently published systematic review and meta-analysis, the coagulation necrosis sign demonstrated the highest area under curve and specificity in differentiating between malignant and benign mediastinal lymphadenopathy.[6] Granulomatous mediastinal lymphadenopathy (TB/sarcoidosis) is

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From the Departments of *Pulmonary, Critical Care and Sleep Medicine; and †Biostatistics, All India Institute of Medical Sciences (AIIMS), New Delhi, India.
K.M. and M.M. contributed equally and are the joint first authors.
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Correspondence: Karan Madan, MD, DM, Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, 110029, India (e-mail: drkaranmadan@gmail.com).

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a major indication for referral for EBUS-TBNA. In a TB endemic setting study, heterogeneous echotexture and coagulation necrosis sign were significantly higher in TB than sarcoidosis.[7] On the other hand, in another study from a similar setting (46 subjects), coagulation necrosis sign was significantly more common in malignant lymph nodes when compared with TB.[8]

A review of the available literature indicates a lack of data on the utility of ultrasonographic lymph node features in differentiating TB and malignant mediastinal lymphadenopathy. There are different observations, especially regarding the coagulation necrosis sign. Our study aimed to compare the various ultrasonographic lymph node characteristics between subjects diagnosed with tuberculous and malignant mediastinal lymphadenopathy.

METHODS

We performed a retrospective and prospective analysis of the EBUS-TBNA database at our facility. EBUS-TBNA is being performed at our facility since 2012. Subjects with a definitive diagnosis of tuberculous or malignant mediastinal lymphadenopathy were included, and their data were extracted from the available records. The data on ultrasonographic features are regularly recorded since the initiation of EBUS-TBNA at our center, and the majority of the data was prospectively collected. The procedure videos are maintained in an electronic database, and the same was reviewed if any additional information was required. Informed consent to participate in the study was obtained. The institute ethics committee approved the study protocol (IEC-PG-45/23.01).

EBUS-TBNA was performed in the bronchoscopy suite using the Olympus BF-UC-180F bronchoscope, with EUME1 and EUME2 ultrasound processor systems. The majority of procedures were performed through the oral route under moderate, proceduralist directed sedation. Few subjects underwent the procedure under general anesthesia after placement of a supraglottic airway device. Intravenous sedation included a combination of midazolam and fentanyl. Ten percent lignocaine spray was applied to the pharynx. Topical anesthesia to the vocal cords and the tracheobronchial tree was achieved using either a "spray as you go technique" or cricothyroid injection of lignocaine solution. Both 21 and 22-G needles were used. Rapid on-site evaluation (ROSE) was performed by either a cytopathologist or a pulmonologist. A minimum of 3 aspirates were obtained from each lymph node station. Glass slide fixed smears were prepared, and cell blocks were also processed. In patients with suspected granulomatous lymphadenopathy, aspirates were also processed for microbiological investigations that included AFB smears, Xpert Mtb RIF test, and mycobacterial liquid cultures. A diagnosis of TB was made if any microbiological investigation for TB was positive. TB was also diagnosed if the cytopathologic examination showed necrotizing granulomatous inflammation along with a compatible clinico-radiologic profile. Other conditions like fungal infection were excluded based on a careful review of clinical radiologic profile. Response to treatment was also noted, and patients were followed up for 6 months to ascertain the final diagnosis. Although, we did use extranodal microbiologic tests to make a final diagnosis, most of our patients were isolated intrathoracic lymphadenitis. Malignancy was diagnosed when the cytopathologic analysis of the aspirates demonstrated malignant cells.

The ultrasonographic lymph node characteristics were recorded before lymph node aspiration. The various features documented included size, shape, margins, calcification, homogeneity or heterogeneous echotexture, central hilar structure, central intranodal vessel, and coagulation necrosis sign, as previously described.[4,9] Size of lymph nodes was documented in both short and long axis. Lymph node shape was defined as round if the long axis/short axis diameter was <1.5, and for oval node, it was >1.5. Margins were labelled as distinct if clearly visible with high echogenicity for $>50\%$ of the boundary. Calcification was defined as a hyperechoic structure with acoustic shadow. Homogenous or heterogeneous echotexture was classified subjectively based on the grayscale appearance and defined as multiple low echoic spots within the lymph node.[10] Coagulation necrosis sign was described as a hypoechoic area within the lymph node without blood flow. The central hilar structure was a hyperechoic flat line often related to the lymph node periphery, representing the hilum of the lymph node. Conglomeration was defined as present when more than one lymph node was visualized at a single lymph node station.[10] Central intranodal vessel sign is defined as the presence of a well-defined smooth hyperechoic wall that was >1 mm in diameter, located toward the center of the lymph node, and demonstrated blood flow on color Doppler.[11] The representative images of the various sonographic characteristics is provided in the Figure 1. The

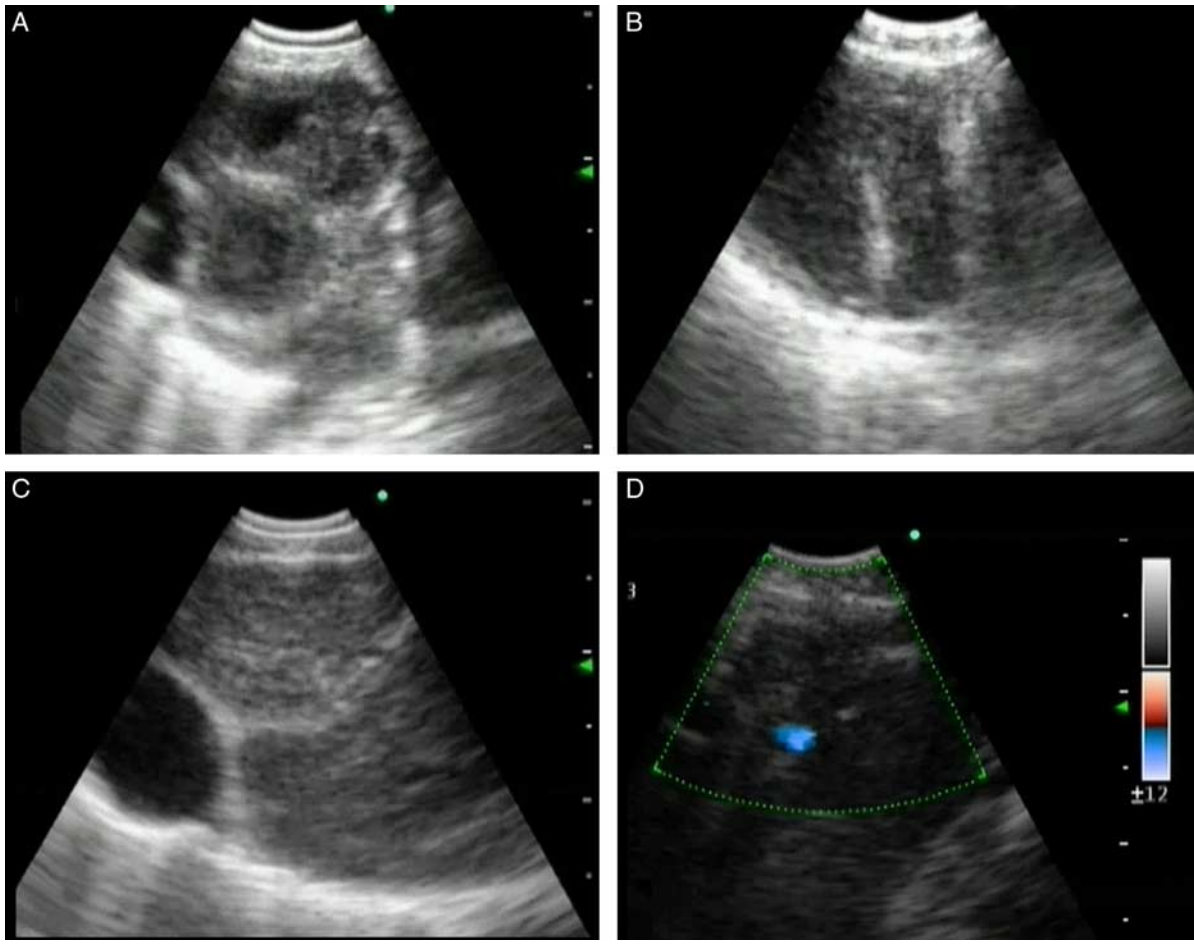

FIGURE 1. Figure depicting the various ultrasonographic lymph node characteristics. A, Coagulation necrosis sign. B, Central hilar structure. C, Homogenous, conglomerated nodes. D, Central intranodal vessel on color doppler.

sonographic features were recorded based on an agreement between at least 2 reviewers. The characteristics of the most prominent and the primarily sampled lymph node were recorded.

Statistical Analysis

The demographic details and ultrasonographic characteristics were recorded in the RedCap data management system. Subjects with complete data of cytopathology and microbiological reports, and ultrasonographic features, were included in the analysis. Statistical analyses were performed using the Stata 16 package (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Categorical variables were summarized as numbers (percentages), while quantitative variables as mean (SD) or median (interquartile range). The χ^2 test was used for comparing categorical variables. The optimal cut-off was determined using the receiver operator curve (ROC) for continuous variables like mean lymph node size. Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, and likelihood ratios were determined for the various ultrasonographic characteristics to differentiate TB from malignancy.

RESULTS

Following a screening of our available database retrospectively and prospective enrollment, 1086 subjects were included. Of these, 547 (50.3%) patients had a diagnosis of TB, and 539 (49.6%) were a malignant diagnosis. The mean age of the cohort was 46.2 (17.11) years. Patients diagnosed with TB were younger, mean age, 37.4 (16.3) years compared with malignancy, 55.2 (12.7) years. The baseline characteristics are summarized in Table 1. The computed tomography (CT) lymph node size (short axis) of the study population [mean (SD)] was 16.2 (7.25) mm, with 15.4 (6.02) mm for tuberculous nodes and 17.1 (8.47) mm for malignant nodes. Heterogenous lymph node appearance on CT scan was more commonly seen in

TABLE 1. Baseline Characteristics of the Subjects in 2 Groups, Malignant and Tuberculous Lymphadenopathy

Parameter	Malignancy, N = 539	Tuberculosis, N = 547
Age (y), mean (SD)	55.2 (12.7)	37.4 (16.28)
Male, n (%)	394 (73.1)	298 (54.48)
Primary approach, n (%)		
EBUS-TBNA	500 (92.8)	533 (97.4)
EUS-B-FNA	39 (7.2)	14 (2.6)
CT Node Short axis diameter (mm), mean (SD)	17.1 (8.47)	15.4 (6.02)
CT Node Long axis diameter (mm), mean (SD)	18.9 (9.1)	17.3 (6.96)
EBUS node short axis diameter (mm), mean (SD)	17.9 (7.91)	16.3 (5.87)
EBUS node long axis diameter (mm), mean (SD)	21.4 (8.84)	19.4 (6.39)

EBUS-TBNA indicates endobronchial ultrasound-guided transbronchial needle aspiration; EUS-B-FNA, transesophageal bronchoscopic ultrasound-guided fine-needle aspiration.

tuberculous nodes (45.22% vs. 27.33%). Lymph node calcification on CT scan was also more common in TB (4.82% vs. 0.87%). The median number of lymph node stations sampled was 1 (1 to 5). The majority of the procedures were performed under moderate sedation (99.3%).

The data on the comparison of ultrasonographic characteristics between the 2 groups are summarized in Table 2. Univariate analysis showed indistinct margins, homogenous echotexture, absent coagulation necrosis sign, absent central hilar structure, absent calcification, absent conglomeration, sonographic lymph node short-axis diameter >16 mm, and node long axis diameter >19 mm were significantly more common in malignancy. In the multivariate analysis, indistinct margins, absent calcification, absent central hilar structure, absent coagulation necrosis sign, absent conglomeration, presence of central intranodal vessel, and sonographic lymph node short-axis diameter >16 mm predicated malignancy. Among these, the adjusted OR was greatest for the absence of conglomeration [4.74 (3.15 to 7.04)] for differentiating malignancy from TB.

Table 3 summarizes the diagnostic accuracy of various ultrasonographic lymph node characteristics to differentiate between malignant and tuberculous mediastinal lymphadenopathy. The highest sensitivity was for the absence of calcification [98.5% (97.1 to 99.4)], while the highest specificity [84.3% (81.0 to 87.2)] was for the presence of central intranodal vessel for a diagnosis of malignancy versus TB. The overall diagnostic accuracy was highest (0.61) for the absence of conglomeration to predict malignancy versus tuberculous mediastinal lymphadenopathy.

DISCUSSION

We have described the utility of ultrasound image characteristics of intrathoracic lymph nodes studied during EBUS-TBNA for differentiating between malignant and tuberculous mediastinal lymphadenopathy. We also report the diagnostic accuracy of specific lymph node characteristics, which may have a utility to predict malignancy. The strengths of this study include a large size patient data set, rigorous diagnostic algorithm and carefully selected diagnostic categories that prevent overlap with other conditions. The findings of the study are representative of the actual life practice of EBUS-TBNA.

A critical observation in this study was finding the poor performance of the coagulation necrosis sign to diagnose malignancy. In the initially described work by Fujiwara et al,[4] the presence of a coagulation necrosis sign demonstrated the highest diagnostic accuracy for a metastatic lymph node. Indeed, this finding may be relevant in settings where TB is uncommon. However, the results of our study indicate that the presence of a coagulation necrosis sign is a more robust indicator for TB than metastasis, especially in TB endemic settings. Necrotic lymph nodes may also represent a diagnosis of metastasis in TB endemic settings, but their presence is more common in TB.[12] In our study, 13.7% of metastatic nodes versus 37.5% tuberculous nodes demonstrated the presence of coagulation necrosis. The findings of our study are also contrary to the observations in a recent meta-analysis, where coagulation necrosis sign was the most specific characteristic in differentiating malignant from benign nodes.[6] The likely reason being that most previous studies are from low TB prevalence settings. One study described the comparative characteristics of sonographic features of malignant versus tubercular nodes. The authors observed distinct margins, absence of central hilar structure, and presence of coagulation necrosis sign as features

TABLE 2. Comparison of Ultrasonographic Lymph Node Characteristics of Malignant and Tubercular Mediastinal Lymphadenopathy

	Malignancy, N = 539	Tuberculosis, N = 547	*P*	*P* Multivariate	Adjusted OR (95% CI)
LN shape					
Round	377 (69.9)	353 (64.5)	0.058	—	—
Oval	162 (30.1)	194 (35.4)			
LN margins					
Distinct	376 (69.8)	456 (83.5)	< 0.001	< 0.001	0.45 (0.32-0.62)
Indistinct	163 (30.2)	91 (16.5)			
LN echotexture					
Heterogenous	304 (56.4)	361 (66.0)	< 0.01	—	—
Homogenous	235 (43.6)	186 (34.0)			
LN calcification					
Absent	531 (98.5)	519 (94.8)	< 0.01	< 0.01	3.52 (1.52-8.14)
Present	8 (1.5)	28 (5.1)			
Central hilar structure (CHS)					
Absent	525 (97.4)	502 (91.8)	< 0.001	< 0.01	2.87 (1.48-5.57)
Present	14 (2.6)	45 (8.2)			
Coagulation necrosis sign (CNS)					
Present	74 (13.7)	205 (37.5)	< 0.001	< 0.001	0.28 (0.20-0.39)
Absent	465 (86.3)	342 (62.5)			
LN conglomeration					
Absent	500 (92.8)	380 (69.5)	< 0.001	< 0.001	4.74 (3.15-7.04)
Present	39 (7.2)	167 (30.5)			
LN central intranodal vessel (CIV)					
Present	108 (20.0)	87 (15.8)	0.063	0.04	1.46 (1.02-2.08)
Absent	431 (80.0)	460 (84.2)			
EBUS node short axis diameter (> 16 mm)					
Yes	291 (55.6)	259 (47.3)	< 0.01	< 0.01	1.54 (1.17-2.01)
No	232 (44.3)	288 (52.6)			
EBUS node long axis diameter (> 19 mm)					
Yes	297 (56.8)	264 (48.2)	< 0.01	—	—
No	226 (43.2)	283 (51.7)			

Data is represented as a number (percentage).
CI indicates confidence interval; EBUS, endobronchial ultrasound; LN, lymph node; OR, odds ratio.

that favored malignancy over TB. However, the study had a small sample size (46 subjects), therefore with a possibility of selection bias.[8]

Studies from low TB prevalence settings have described round shape, distinct margins, and heterogeneous echotexture more commonly in malignancy.[4] In another systematic review, the absence of central hilar structure and heterogeneous echotexture were associated with malignancy.[5] The comparative group in these studies was benign lymphadenopathy and not specifically TB. Heterogeneous echotexture has previously been described to favor a diagnosis of TB over sarcoidosis.[7] Therefore, the findings of our study highlight that the results of heterogeneous echotexture and coagulation necrosis signs may be taken as predictors with consideration of TB versus malignancy and necessitate lymph node aspiration to differentiate between the 2 conditions. The sonographic characteristics do not replace the requirement of lymph node aspiration. The first differential diagnostic consideration over the another shall depend on the prevalence of TB in the study population.

Another feature that has been described to predict malignant nodes is the absence of a central intranodal vessel.[13] However, we observed that the absent central intranodal vessel sign was more common in TB. Of all the sonographic characteristics, the highest diagnostic accuracy (0.61) was found for the absence of nodal conglomeration, which is not sufficiently encouraging. Therefore, the prediction potential of ultrasonographic features in differentiating malignancy from TB is poor. The ultrasonographic imaging features of lymph nodes studied during EBUS-TBNA are insufficient in themselves to avoid lymph node aspiration.

Apart from sonographic characteristics, another imaging modality during EBUS is elastography. A recent meta-analysis concluded that elastography might help differentiate malignant from benign lymph nodes, but lymph node aspiration is still required.[14,15] It has also been highlighted

TABLE 3. Diagnostic Accuracy Parameters of Various Ultrasonographic Lymph Node Characteristics to Differentiate Malignant From Tubercular Mediastinal Lymphadenopathy

	SN	SP	PPV	NPV	PLR	NLR	DOR	Diagnostic Accuracy
Distinct margins	69.8% (65.7-73.6)	16.6% (13.6-20)	45.2% (41.8-48.6)	35.8% (29.9-42.1)	0.84 (0.78-0.89)	1.82 (1.45-2.28)	0.46 (0.34-0.62)	0.43
Heterogenous echotexture	56.4% (52.1-60.6)	34% (30-38.1)	45.7% (41.9-49.6)	44.2% (39.4-49.1)	0.85 (0.78-0.94)	1.28 (1.10-1.48)	0.67 (0.52-0.85)	0.45
Absence of calcification	98.5% (97.1-99.4)	5.1% (3.4-7.3)	50.6% (47.5-53.6)	77.8% (60.8-89.6)	1.04 (1.02-1.06)	0.30 (0.14-0.65)	3.58 (1.65-7.78)	0.51
Absence of central hilar structure	97.4% (95.7-98.6)	8.2% (6.1-10.9)	51.1% (48-54.2)	76.3% (63.4-85.4)	1.06 (1.03-1.09)	0.30 (0.16-0.55)	3.36 (1.84-6.15)	0.52
Presence of coagulation necrosis sign	13.7% (10.9-16.9)	62.5% (58.3-66.6)	26.5% (21.4-32.1)	42.4% (38.9-45.9)	0.37 (0.29-0.46)	1.38 (1.28-1.48)	0.27 (0.20-0.36)	0.38
Absence of conglomeration	92.8% (90.2-94.8)	30.5% (26.7-34.6)	56.8% (53.5-60.1)	81.1% (75-86.2)	1.34 (1.26-1.42)	0.23 (0.16-0.32)	5.63 (3.89-8.11)	0.61
Presence of central intranodal vessel	20% (16.7-23.7)	84.3% (81-87.2)	55.7% (48.4-62.8)	51.7% (48.3-55)	1.27 (0.99-1.65)	0.95 (0.90-1.0)	1.34 (0.98-1.83)	0.52
EBUS node short axis diameter (> 16 mm)	55.5% (51.2-59.7)	52.7% (48.4-56.9)	53.6% (49.3-57.8)	54.5% (50.2-58.9)	1.17 (1.04-1.32)	0.85 (0.75-0.96)	1.39 (1.09-1.76)	0.53 AUC 0.54
EBUS node long axis diameter (> 19 mm)	56.8% (52.5-61.0)	51.7% (47.5-56)	53.7% (49.5-57.8)	54.8% (50.4-59.4)	1.18 (1.05-1.32)	0.84 (0.74-0.95)	1.41 (1.11-1.79)	0.53 AUC 0.54

Values within parenthesis represents 95% confidence interval.

DOR indicates diagnostic odds ratio; EBUS, endobronchial ultrasound; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; SN, sensitivity; SP, specificity.

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that the performance characteristics of elastography may be variable, with a significant overlap between malignant and benign node features in settings where granulomatous nodes are common.[16]

A combination of sonographic characteristics may be more useful in predicting malignancy than either sign alone. The Canada Lymph Node Score (a 4-point score including the parameters: short-axis diameter, margins, central hilar structure, and necrosis) demonstrated good performance for identification of malignant lymphadenopathy.[17] Such multiparameter scores require prospective validation in larger data sets from varying regions.

Our study has limitations. We performed a per-patient analysis rather than a per node analysis (which was desirable but not feasible owing to the study design). Therefore, the sonographic characteristics of the "most abnormal" or the primarily sampled node were recorded. We did not analyze the data based on the histopathologic subtype of malignancy. For some patients, data was extracted after a review of the video data set retrospectively. Patients with insufficient data were excluded from the study.

CONCLUSION

Further research is required to improve the image analysis modalities in EBUS-TBNA to have sufficient diagnostic accuracy. Future studies should also focus on newer image interpretation methods along with the integration of multiple processes simultaneously. The presence of coagulation necrosis sign and heterogenous lymph node echotexture may not predict malignant nodes, especially in settings where the prevalence of TB is high.

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