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Endobronchial ultrasound sonographic characteristics of mediastinal lymph node in the evaluation of lung cancer

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Abstract

Endobronchial ultrasound (EBUS) and contrast-enhanced computed tomography (CECT) are essential components of lung cancer evaluation. Features of mediastinal lymph nodes on EBUS and CECT can help in predicting metastatic disease. Clinical, radiological, and EBUS data of patients with clinico-radiological suspicion of lung cancer who have undergone EBUS with no transbronchial needle aspiration (TBNA) or nonyielding EBUS-TBNA were retrospectively collected from medical records. EBUS features of lymph nodes for metastatic disease [size >1 cm, round shape, heterogeneous echotexture, indistinct margin, coagulation necrosis (CN), absence of central hilar structures (CHS), and grade II-III vascularity] were noted. CECT findings were noted from CECT films and reports to analyze and compare with EBUS findings. Scoring criteria of EBUS sonographic characteristics from previous studies for discriminating benign and malignant lymph nodes were also assessed for possible prediction. 31 patients [male: 18 (58.1%), female: 13 (41.9); age (mean ± standard deviation): 52.9±15.7 years] with CECT findings suggesting lung cancer were studied. EBUS showed mediastinal lymphadenopathy at 82 lymph node stations in 29 patients. Size >1 cm, round shape, heterogeneous echotexture, distinct margin, CN, absence of CHS and grade II-III vascularity at 33 (40%), 28 (34%), 31 (38%), 55 (67%), 3 (4%), 77 (94%), and 6 (7.3%) lymph nodes, respectively, were found. The malignant or benign status assigned to lymph nodes using different scoring criteria was highly discordant. Compared to EBUS, CECT revealed abnormal mediastinal lymph nodes in significantly fewer patients [21 (67.7%) *versus* 29 (93.5%), p=0.01] involving a lower number of lymph node stations (37 *versus* 82, p<0.001). Lymphadenopathy frequency at different LNS on EBUS and CECT showed a weak positive but significant correlation (r=0.356; p=0.0426). EBUS characteristics and related scores have limited accuracy in differentiating benign and malignant nodes. CECT underestimates lymphadenopathy in comparison to EBUS. A larger prospective study of EBUS features with cyto/histopathology correlation may elicit its clinical significance and help to create better and more composite scoring criteria.

Introduction

The introduction of endobronchial ultrasound (EBUS) in 2002 revolutionized the diagnosis and staging of lung cancer by replacing conventional transbronchial needle aspiration (TBNA) and even mediastinoscopy. With an increasing pool of evidence for

about a decade, EBUS-TBNA has been recommended in the 2013 American College of Chest Physicians guidelines for lung cancer as a first-line intervention for invasive mediastinal staging of non-small cell lung cancer [1]. EBUS and contrast-enhanced computed tomography (CECT) are essential components of lung cancer evaluation. Features of mediastinal lymph nodes (LNs) on EBUS and CECT can help in predicting metastatic disease [2,3].

A well-accepted criterion for an abnormal LN on computed tomography (CT) images is an axial short-axis diameter (SAD) of 1 cm or greater. Certain features may also raise suspicion of metastatic involvement, even in sub-centimetric LNs – abnormal shape or attenuation of the LN or multiple LNs in a group. However, CT is relatively inaccurate for identifying pathologic mediastinal lymphadenopathy (sensitivity, 51-64%; specificity, 74-86%) [3]. EBUS characteristics of LNs shown in several studies to be predictive of malignancy with variable accuracy are size, shape, margin, echogenicity, central hilar structure (CHS), coagulation necrosis (CN), and vascularity [4-9]. In this study, we have used various EBUS features and related scoring criteria to identify LNs with high or low risks for malignancy where EBUS-TBNA investigation results were lacking.

Materials and Methods

Selection and description of participants

This retrospective study included all patients subjected to EBUS at our institute between August 2021 and July 2022, where TBNA was non-yielding or not done. This study aims to evaluate mediastinal LN for sonographic features on EBUS to predict their malignant potential, along with a comparison with CECT findings. Records of these patients were reviewed, and data was collected from case files, CECT thorax films and reports, EBUS images, and reports. Patients' clinical data, *e.g.*, age, gender, and provisional diagnosis, was retrieved from the case files. From CECT films and reports, data pertaining to LN station, size (centimetric/subcentimetric), pleural, mediastinal, and/or parenchymal findings were retrieved and compared with EBUS findings.

Technical information

EBUS scope (EB-530US, Fujifilm, Japan) was introduced through oral route under moderate sedation. The EBUS image was processed with an ultrasound processor (Fujifilm processor VP 3500 HD, Japan) at a frequency of 7.5-12 MHz. In every patient, all ten LN stations, *i.e.*, upper paratracheal (2R and 2L), lower paratracheal (4R and 4L), subcarinal (Station 7), hilar (10R and 10L), and interlobar (11Rs, 11Ri, and 11L) LN stations, were screened and assessed for number of LNs, size (SAD), shape, echotexture, margin, CHS, CN, and vascularity. The number of LNs was assessed for single or multiple LN stations. In the presence of multiple LN characters, the largest LN was noted. SAD was measured and the high risk for malignancy was defined as a size >10 mm [4,6-9]. Shapes were assessed as round or oval where round shape was defined as a ratio <1.5 for long and SAD [4,6]. The margin of LNs was defined as distinct when >50% border was clearly visualized [4,6]. Echotextures of LNs were assessed as homogeneous or heterogeneous; whereas, the presence of multiple hypo-echoic areas in LNs was defined as heterogeneous [4,6]. CN was defined as the presence of a few hypo-echoic areas without vascularity [4,6]. CHS was defined as the presence of a linear, flat, hyper-echoic area in the center of LN [4,6]. Vascularity of LN on color doppler mode was defined as grade 0, no blood flow or small amounts of flow; grade I, a few main vessels running toward the center of the LN from the hilum; grade II, a few punctiform or rod-shaped flow signals, and a few small vessels found as a long strip of a curve; and grade III, rich flow, more than four vessels found with different diameters and a twist or helical-flow signal [5]. The frequency of various lymph nodal characters was compared with previous study results. The following scoring criteria from previous studies were used in an attempt to identify each LN with high malignant potential: i) Fujiwara *et al*. identified round shape, distinct margin, heterogeneous echogenicity, and the CN sign as features of malignant LN [4]; 43% of LNs having at least one character were malignant; when all four signs were absent, the negative predictive value was 96%; ii) Ayub *et al.* identified the presence of a combination of distinct margin, CHS, and nodal conglomeration as predictor of benign LN [6]; all LNs with all three benign characteristics were benign; 36.4% were malignant as all three characters were absent and were malignant; iii) in Shafiek *et al*., presence of margin distinction, round shape, and SAD ≥10 mm were assigned a score of 1, and heterogeneous echogenicity and absence of CHS were assigned a score of 1.5; a total score >5 predicted LN malignancy [8]; iv) Schmid-Bindert *et al*. identified nodal characters of short axis >1 cm, heterogeneous pattern, round shape, distinct margin, absence of a CHS and high blood flow in an LN as predictors of malignant LN; the odds of malignant LN were 15.5 in the presence of two or more characters [9].

Statistical methods

All the data was analyzed using SPSS version 20 software (IBM, Armonk, NY, USA). Categorical data was analyzed by Pearson chi-square test and quantitative data was analyzed by Student's *t*-test. Correlation between two parameters was seen with the Spearman's rank correlation test. A p-value of less than 0.05 was considered as the level of significance for all statistical tests.

Results

This study included 31 patients with an age (mean ± standard deviation) of 52.9±15.7 years. 18 (58.1%) patients were male and 13 (41.9%) were female. CECT showed lung mass in 17 (54.8%) patients, pleural effusion (low adenosine deaminase and high mesothelial cell count) in 12 (38.7%), partial lung collapse in 3 (9.7%), and mediastinal mass in 3 (9.7%) (Table 1). In CECT, significantly enlarged LNs were present at 37 LN stations in 21 (67.7%) patients. Stations 7 and 4R were commonly involved LN stations and were seen in 15 (48.4%) and 13 (41.9%) patients, respectively (Figure 1A). 6 LN stations had sub-centimetric LNs. At 82 LN stations, EBUS showed lymphadenopathy. LN stations 7, 4R, 11R, and 4L were frequently involved LN stations and were seen in 24 (29.2%), 22 (26.8%), 12 (14.6%), and 14 (17.1%) patients, respectively (Figure 1A). Multiple LNs were present at 13 LN stations, with station 7 being the most commonly involved in 10 (32.25%) patients. EBUS showed LNs with SAD greater than 1 cm at 33 (40%) LN stations. 18 (22%) LN stations had LN sizes less than 5 mm (Figure 1B). Round and oval-shaped nodes were present at 28 (34%) and 54 (66%) LN stations, respectively (Table 2). EBUS showed round, oval, and both oval and round nodes in 5 (16%), 11 (33%), and 13 (42%) patients, respectively. A distinct margin was present in the EBUS image of LN at 55 (67%) LN stations (Table 2). In 31 (38%) LNs, heterogeneous echotexture was present in the EBUS image (Table 2). EBUS showed LNs with

CHS and CN in LNs at 5 (6%) and 3 (4%) LN stations, respectively (Table 2). EBUS color doppler showed vascularity of grade 0, grade I, grade II and grade III in 30 (36.6%), 46 (56.1%), 4 (4.9%), and 2 (2.4%) LNs, respectively. Compared to EBUS, CECT revealed lymphadenopathy in a significantly smaller number of patients [21 (67.7%) *versus* 29 (93.5%), p=0.01], involving a significantly smaller number of LN stations (37 *versus* 82, p<0.001) (Figure 1A). At the commonest involved LNS, CECT elicited significantly less frequent involvement in comparison with EBUS at subcarinal (15 *versus* 24, p=0.018) and pre-carinal/right paratracheal (13 *versus* 22, p=0.021) stations. Spearman rank correlation test was done to compare the frequency of various LN station involvement on CECT and EBUS, which showed a significant but weak positive correlation (r=0.356, p=0.043) (Figure 2). The correlation between the sizes of LNs measured on CECT and EBUS was tested when LNs were seen on both. No significant correlation was seen between CECT and EBUS for LN size (r=0.246, p=0.181).

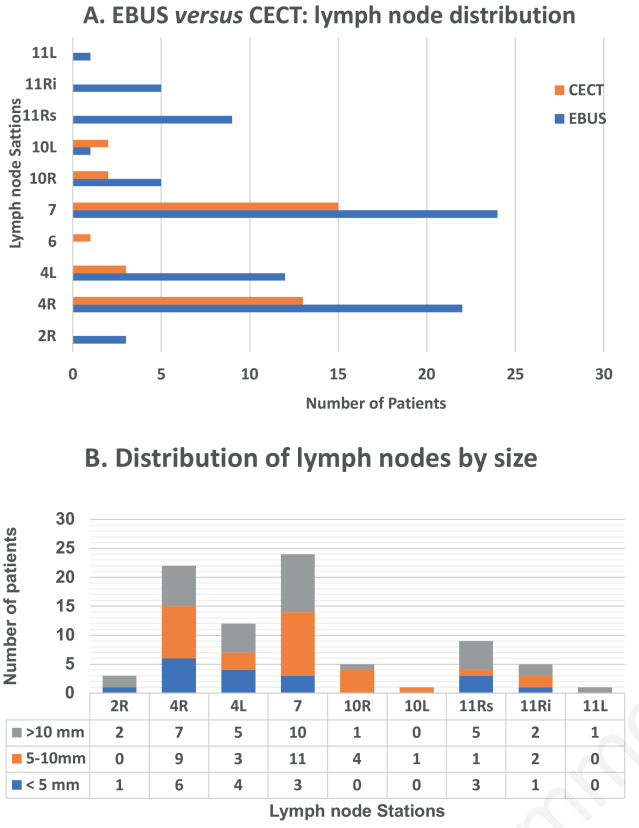

Figure 1. A) Comparison of frequency of distribution of lymph nodes at various lymph node stations in contrast-enhanced computed tomography (CECT) and endobronchial ultrasound (EBUS); B) distribution of lymph nodes by size involving various lymph node stations in EBUS.

Discussions

The CHEST guidelines and the expert panel report CHEST

Table 1. Patient baseline data and contrast-enhanced computed tomography findings.

Patient characteristics	(n=31)
Age (mean±SD, years)	52.9±15.7
Gender, n (%)	
Male	18 (58)
Female	13 (42)
CECT thorax, n (%)	
Lung mass	17 (54.8)
Mediastinal mass	3 (9.7)
Pleural effusion	12 (38.7)
Collapse	3 (9.7)
Lymphadenopathy	21 (67.7)
Right lower paratracheal	13 (41.9)
Left lower paratracheal	3 (8.1)
Subcarinal	15 (48.4)
Right hilar	3 (8.1)
Left hilar	2 (6.5)
Para-aortic	1 (3.2)

SD, standard deviation; CECT, contrast-enhanced computed tomography.

Table 2. Frequency of lymph nodes endobronchial ultrasound sonographic features (n=82).

EBUS features	Malignant features, n (%)	Benign features, n (%)
Size	>10 mm 33 (40)	<10 mm 49 (60%)
Shape	Round 28 (34)	Oval 54 (66)
Margin	Distinct 55 (67)	Indistinct 27 (33)
Echotexture	Heterogenous 31 (38)	Homogenous 51 (62)
Central hilar structure	Absent 77 (94)	Present 5 (6)
Coagulation necrosis sign	Present 3 (4)	Absent 79 (96)
Vascularity	Grade II and III 6 (7.3)	Grade 0 and I 76 (92.7%)

EBUS, endobronchial ultrasound.

2016 stated that EBUS ultrasonographic features of LNs can be used to predict malignant and benign diagnoses, but tissue samples should still be obtained to confirm a diagnosis [10]. A situation may arise when multiple enlarged LNs are present at a station or different stations in a patient, and sampling of all nodes may not be practical. Using these criteria to choose LNs for sampling further stresses the utility of having such criteria. In the last two decades, many studies have shown that malignant LN features on EBUS studied in various studies have variable accuracy [4-9].

Memoli *et al.* showed that increased size and a round or oval shape are risk factors for malignancy [7]. Fujiwara *et al.* reported four features as independent risk factors for malignancy: round shape, distinct margin, heterogeneous echogenicity, and the CN sign [4]. In that study, the frequency of malignant features was significantly higher in malignant nodes compared to benign nodes. The frequencies of various LN characters seen on EBUS in our study are close to the average frequency seen in malignant and benign nodes in the Fujiwara *et al.* study [4], except for CHS and CN, which are less frequently reported in our study (Figure 3). Fujiwara *et al.* showed that 43% of LNs having at least one of the above-mentioned four characters proved to be malignant. When all four signs were absent, the negative predictive value was 96% [4]. In our study, 72 LNs had at least one malignant character present. Two LNs with all four malignant features were found in two different patients. One of them had a right hilar mass but the other had isolated mediastinal tubercular lymphadenopathy (later confirmed to be tubercular). 10 LN had all four malignant characters absent, but only one patient with all nodes with such benign features had a right lower lobe lung mass.

Contrary to Fujiwara *et al*. [4], an Indian study by Ayub *et al.* found that the frequency of heterogeneous echotexture, distinct margin, and CN were not significantly different in benign and malignant LNs [6]. This can be partly explained by the high prevalence of tuberculosis in this region. This can also be viewed with the findings of another Indian study by Dhooria *et al*. [11], where heterogeneous echotexture (53.4% *versus* 12.6%, p<0.001) and CN (26.1% *versus* 3.3%; p<0.001) were significantly higher in tuberculous LN in comparison to sarcoidosis LN. CHS and nodal conglomeration are significantly more frequently seen in benign nodes in the Ayub *et al.* study [6]. Logistic regression analysis in the study by Ayub *et al.* revealed that the simultaneous presence of distinct margin, CHS, and nodal conglomeration is a predictor of benign LN [6]. LNs with all three benign characteristics were found to be benign, and when all three characters were absent, 36.4% were found to be malignant. In comparison with the study by Ayub *et al.*, LNs in our study had heterogeneous echotexture that was more frequent, but other characters such as distinct margin, CN, conglomeration, and CHS were less frequently observed (Figure 2). In our study, 9 (11%) LNs had all three benign characters present (but no patient had only such nodes). Only one LN had all three benign characteristics absent. No concordance was seen among LNs with benign features identified using Fujiwara *et al.* study criteria (10 LNs with benign features) and Ayub *et al.* study criteria (9 LNs with benign features) [4,6].

Shafiek *et al*. made a simplified score: heterogeneous echogenicity and absence of CHS were given a score of 1.5, and the presence of margin distinction, round shape, and SAD≥10 mm were given a score of 1 [8]. A total score >5 predicted LN malignancy (sensitivity 78% and specificity 86%). In our study, 4 LN from four patients had scores >5. On CECT, those four patients had right upper lobe mass, right hilar mass, mediastinal mass, and isolated mediastinal tubercular lymphadenopathy, respectively. In a study by Nakajima *et al.* [5], defining grades II and III as "malignant," the sensitivity, specificity, and diagnostic accuracy rates were 88%, 70%, and 78%, respectively. In our study, 6 (7.3%) LNs had grade II or III vascularity. On comparing nodes with malignant features in the studies by Shafiek *et al*. [8], and Nakajima *et al.* [5], all patients except one were discordant. In a study by Schmid-Bindert *et al.* (n=145, LNs studied 281) [9], nodal characters of short axis >1 cm, heterogeneous pattern, round shape, distinct margin, absence of a CHS and high (grades II and III) blood flow in an LN were studied. The positive predictive value was best for heterogeneity (73%), with a negative predictive value of more than 80%. The sum score resulted in an odds ratio of 15.5 if more than two

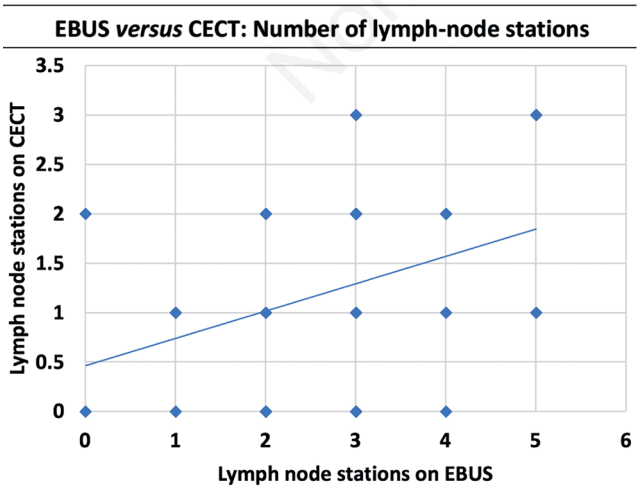

Figure 2. Spearman rank correlation test between contrast-enhanced computed tomography (CECT) and endobronchial ultrasound (EBUS) showing a significant but weak correlation of lymph node stations involved.

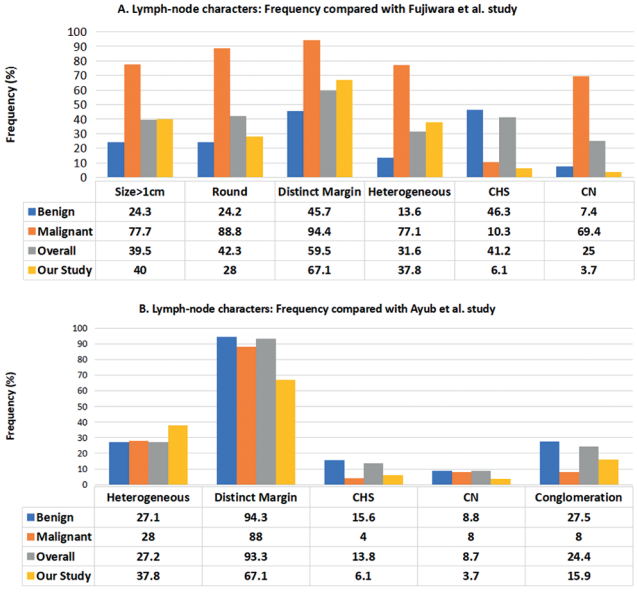

Figure 3. Comparison of frequency of lymph node features in endobronchial ultrasound with previous studies. CHS, central hilar structures; CN, coagulation necrosis.

criteria were positive (p<0.00001). In our study, 47 LNs from 24 patients had more than two malignant characters.

Based on various study scoring criteria for benign or malignant risks, LNs in our study were variably placed as LNs with benign or malignant features, making it difficult to predict anything with accuracy. This makes cytopathologic and histopathologic evaluations indispensable at present. Other malignant risk predictors that are not in the scope of this study, *e.g.*, CT texture analysis, positron emission tomography (PET)-CT, and EBUS elastography, have been studied in the recent past and have shown good accuracy [12-16]. Estimation of a composite pre-EBUS likelihood by calculating clinical risks and radiological risks based on PET-CT and CT texture analysis along with EBUS elastography, color power Doppler imaging, and other sonographic features may yield a more robust predictor of malignant LNs with acceptable accuracy.

Being a retrospective study, our study has many limitations. As it includes only those patients whose EBUS-TBNA cytology and histopathological results were lacking, not having a gold standard for comparison is the major limiting factor. Limited follow-up data of only a few patients is available. The sample size of the study is small. Many EBUS image findings can have interobserver variability, which was inevitable. All the EBUS image interpretation has been done by one pulmonologist with significant previous experience doing EBUS to decrease likely bias.

Conclusions

EBUS characteristics and related scores have limited accuracy in differentiating benign and malignant nodes. In comparison to EBUS, CECT underestimates lymphadenopathy. A larger prospective study with cyto/histopathological correlation to create a more comprehensive scoring system may be useful.

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