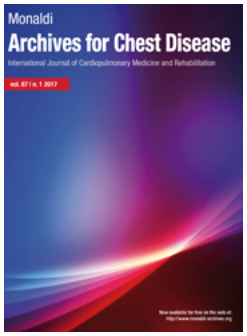

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Endobronchial ultrasound sonographic characteristics of mediastinal lymph node in evaluation of lung cancer

Manoranjan Pattnaik, Jeetendra Kumar Patra, Onkar Kumar Jha

Department of Pulmonary Medicine (Superspeciality-DM), Sriram Chandra Bhanja Medical College and Hospital, Cuttack, Odisha, India

Corresponding Author: Onkar Kumar Jha, Department of Pulmonary Medicine (Superspeciality-DM), Sriram Chandra Bhanja Medical College and Hospital, Mangalabag, Cuttack 753007, Odisha, India. Tel. +919818080333. E-mail: onkarjha@hotmail.com

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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 and have undergone EBUS with no trans-bronchial needle aspiration (TBNA) or nonyielding EBUS-TBNA were retrospectively collected from medical records. EBUS features of lymph nodes for metastatic disease [Size >1cm, round shape, heterogeneous echo-texture, 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 analyse 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. Thirty-one (31) patients [male=18 (58.1%), female=13 (41.9); age (mean±SD) =52.9±15.7 years] with CECT findings suggesting lung cancer were studied. EBUS showed mediastinal lymphadenopathy at 82 lymph node station in 29 patients. Size>1cm, round shape, heterogeneous echo-texture, 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. Malignant or benign status assigned to lymph nodes using different scoring criteria were highly discordant. Compared to EBUS, CECT revealed abnormal mediastinal lymph nodes (LN) in significantly less number of patients [21(67.7%) vs 29 (93.5%), p=0.01] involving less number of lymph node stations (LNS) [(37 vs 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 lymph-adenopathy in comparison to EBUS. Larger prospective study of EBUS features with cyto/histo-pathology correlation may elicit its clinical significance and help to create a better and composite scoring criteria.

Key words: mediastinal lymphadenopathy; EBUS; lung cancer, CECT.

Introduction

After introduction of endo-bronchial ultrasound (EBUS) in 2002, it has revolutionized the diagnosis and staging of lung cancer by replacing conventional transbronchial needle aspiration (TBNA) and even mediastinoscopy. With 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]. Endobronchial ultrasound (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 lymph node 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 lymph nodes - abnormal shape or attenuation of the lymph node, multiple lymph nodes in a group. CT, however, is relatively inaccurate for identifying pathologic mediastinal lymphadenopathy (sensitivity, 51-64%; specificity, 74-86%) [3]. EBUS characteristics of lymph nodes 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 lymph nodes with high or low risks for malignancy where EBUS-TBNA investigation results were lacking .

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. Aim of the study is to evaluate mediastinal lymph node (LN) for sonographic features on EBUS to predict their malignant potential along with a comparison with CECT findings. Record of these patients reviewed and data was collected from case file, CECT thorax films and reports, EBUS images and reports. Patient's clinical data e.g. age, gender and provisional diagnosis was retrieved from case files. From CECT films and reports data pertaining to

lymph node 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. EBUS image was processed with ultrasound processor (Fujifilm processor VP 3500 HD, Japan) at frequency of 7.5 -12 MHz. In every patient all ten lymphnode 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) lymph node stations were screened. All lymph node stations were assessed for number of LN, size (SAD), shape, echo-texture, margin, central hilar structure (CHS), coagulation necrosis (CN) and vascularity. Number of lymph nodes assessed for single or multiple at every lymph node stations (LNS). In presence of multiple lymph nodes characters of the largest lymph node were noted. Short axis diameter measured and high risk for malignancy defined as size >10 mm [4,6-9]. Shapes were assessed as round or oval where round shape was defined as ratio <1.5 for long and short axis diameter [4,6]. Margin of lymph nodes were defined distinct when >50% border is clearly visualized [4,6]. Echo-textures of lymph nodes assessed as homogeneous or heterogeneous where presence of multiple hypo-echoic areas in lymph nodes were defined as heterogeneous [4,6]. Coagulation necrosis was defined as presence of few hypo-echoic areas without vascularity [4,6]. Central hilar structure defined as presence of linear, flat, hyper-echoic area in the centre of lymph node [4,6]. Vascularity of lymph node on color doppler mode defines 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, 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]. Frequency of various lymph nodal characters were compared with previous study results. Following scoring criteria from previous studies were used in an attempt to identify each lymph node with high malignant potential: i) Fujiwara *et al*. [4] identified round shape, distinct margin, heterogeneous echogenicity, and the coagulation necrosis sign as feature of malignant lymph node; 43% of lymph-nodes having at least one character were malignant; when all four signs were absent, negative

predictive value was 96%. ii) Ayub *et al.* [6] identified presence of combination of distinct margin, CHS and nodal conglomeration as predictor of benign LN; All lymph-nodes with all the three benign characteristics were benign and when all the three characters absent 36.4% were malignant. iii) In Shafiek *et al*. [8] score 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 score >5 predicted LN malignancy. iv) Schmid-Bindert *et al*. [9] identified nodal characters of short axis >1cm, heterogeneous pattern, round shape, distinct margin, absence of a central hilar structure and high blood flow in a LN as predictor of malignant lymph node; odds of malignant lymph node was 15.5 in presence of two or more characters.

Statistical methods

All the data was analysed using SPSS version 20 software. Categorical data was analyzed by Pearson chi-square test and quantitative data will be analyzed by Student's *t*-test. Correlation between two parameters was seen with 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

Study included 31 patients with age (mean ± SD) of 52.9±15.7 years. Eighteen (58.1%) patient were male and 13 (41.9%) were female. CECT showed lung mass in 17 (54.8%) patients, pleural effusion (low ADA and high mesothelial cell count) in 12 (38.7%) patients, partial lung collapse in 3 (9.7%) patients and mediastinal mass in 3 (9.7%) patients (Table 1). In CECT significantly enlarged lymph-nodes were present at 37 lymph-node stations of 21 (67.7%) patients. Stations 7 and 4R were commonly involved lymph-node stations and seen in 15 (48.4%) and 13 (41.9%) patient respectively (Figure 1A). 6 lymph-node stations had sub-centimetric lymph-nodes. EBUS showed lymph-adenopathy at 82 lymph-node stations. Lymph-node stations 7, 4R, 11R and 4L were frequently involved lymph node stations and seen in 24 (29.2%), 22 (26.8%), 12 (14.6%) and 14 (17.1%) patients ,respectively (Figure 1A). Multiple LN were present at 13 lymph node station and most commonly involving station 7 in 10 (32.25%) patients. EBUS showed lymph-nodes with SAD more than 1 cm at 33 (40%) lymph-node stations.

Eighteen (22%) lymph-node stations had lymph-node size less than 5 mm (Figure 1B). Round and oval shaped nodes were present at 28(34%) and 54 (66%) lymph-node stations respectively (Table 2). EBUS showed round, oval and both oval as well as round nodes in 5 (16%), 11 (33%) and 13 (42%) patients respectively. Distinct margin present in EBUS image of lymph-node at 55 (67%) LNS(Table 2). In 31 (38%) lymph nodes heterogeneous echo-texture was present in EBUS image (Table 2). EBUS showed lymph-nodes with CHS and CN in lymph-nodes at 5 (6%) and 3 (4%) LNS, respectively (Table 2). EBUS colour 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%) lymph nodes, respectively.

Compared to EBUS, CECT revealed lymph-adenopathy in significantly less number of patients [21 (67.7%) vs 29 (93.5%), p=0.01] involving significantly less number of lymph node stations (LNS) [(37 vs 82, p<0.001] (Figure 1A). At commonest involved LNS, CECT elicited significantly less frequent involvement in comparison with EBUS at subcarinal (15 vs 24, p=0.018) and pre-carinal/right paratracheal (13 vs 22, p=0.021) stations. Spearman rank correlation test was done to compare frequency of various lymph node station involvement on CECT and EBUS which showed a significant but weak positive correlation (=0.356, p =0.043) (Figure 2). Correlation between sizes of lymph nodes measured on CECT and EBUS was tested when lymph nodes were seen on both. No significant correlation was seen between CECT and EBUS for Lymph-node size (r=0.246, p 0.181).

Discussions

CHEST guideline and expert panel report CHEST 2016 recommended EBUS ultrasonographic features of lymph nodes 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 lymph nodes present at a station or at different stations in a patient and sampling of all nodes may not be practical. Using these criteria to choose lymph nodes for sampling further stresses the utility of having such criteria. In last two decade many studies have shown that malignant lymph node features on EBUS studied in various studies have variable accuracy [4-9].

Memoli *et al.* [7] showed that increased size with a round or oval shape are risk factors for malignancy. Fujiwara *et al.* [4] reported 4 features as independent risk factors for

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

Contrary to Fujiwara *et al.* [4], an Indian study by Ayub *et al.* [6] showed frequency of heterogeneous echotexture, distinct margin and coagulation necrosis were not significantly different in benign and malignant lymph nodes. This can be partly explained by high prevalence of tuberculosis in this region. This can also be viewed with findings of another Indian study [11] by Dhooria *et al.*, where heterogeneous echotexture (53.4% vs 12.6%, $p<0.001$) and coagulation necrosis (26.1% vs 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 Ayub *et al.* study [6]. Logistic regression analysis in Ayub *et al.*'s study [6] revealed that simultaneous presence of distinct margin, CHS and nodal conglomeration is predictor of benign LN. Lymph-nodes with all the three benign characteristics were found to be benign and when all the three characters absent 36.4% were found to be malignant. On comparing with Ayub *et al.*'s study lymph nodes in our study had heterogeneous echotexture more frequent but other characters distinct margin, coagulation necrosis, conglomeration and central hilar structure were less frequently observed (Figure 2B). In our study, 9 (11%) Lymph nodes had all the 3 benign characters present (but no patient with only such nodes). Only one lymph node had all the three benign characteristics absent. No concordance was seen among lymph nodes with benign features identified using

Fujiwara *et al*. study criteria (10 lymph nodes with benign features) and Ayub *et al*. study criteria (9 lymph nodes with benign features) [4,6].

Shafiek *et al*. [8] generated a simplified score (presence of margin distinction, round shape and SAD ≥10 mm were scored as 1, and heterogeneous echogenicity and absence of CHS were scored as 1.5). A total score >5 predicted LN malignancy (sensitivity - 78% and specificity -86%). In our study, 4 LN from 4 patients had score >5. On CECT those 4 patients had RUL mass, right hilar mass, mediastinal mass and isolated mediastinal tubercular lymphadenopathy, respectively.

In a study by Nakajima *et al*. [5] defining Grade II and III as "malignant," has the sensitivity, specificity, and diagnostic accuracy rate were 88%, 70%, and 78%, respectively. In our study, 6 (7.3%) lymph nodes had Grade II or III vascularity. On comparing nodes with malignant features in Shafiek *et al*. [8] and Nakajima *et al*. [5] studies, all patient except one were discordant. In a study by Schmid-Bindert *et al*. [9] (n=145, lymph-nodes studied 281) nodal characters of short axis >1cm, heterogeneous pattern, round shape, distinct margin, absence of a central hilar structure and high (grade II and III) blood flow in a LN were studies. 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 criteria were positive ($p<0.00001$). In our study 47 lymph nodes from 24 patients had more had more than 2 malignant characters.

Based on various study scoring criteria for benign or malignant risks, lymph nodes in our study were variably placed as lymph nodes with benign or malignant features making it difficult to predict anything with accuracy. This makes cytopathologic and histopathologic evaluation indispensable at present. Other malignant risk predictors which are not in the scope of this study e.g., CT texture analysis [12,13], positron emission tomography (PET)-CT [14,15] and EBUS elastography [16] have been studied in recent past and have shown good accuracy. Estimation of a composite pre-EBUS likelihood by calculating clinical risks, radiological risks based on PET-CT and CT texture analysis along with EBUS elastography, colour power doppler imaging and other sonographic features may yield a more robust predictor of malignant lymph nodes with acceptable accuracy.

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

Conclusions

EBUS characteristics and related scores have limited accuracy in differentiating benign and malignant nodes. CECT underestimates lymphadenopathy in comparison to EBUS. Larger prospective study with cyto/histo-pathological correlation to create more comprehensive scoring system may be useful.

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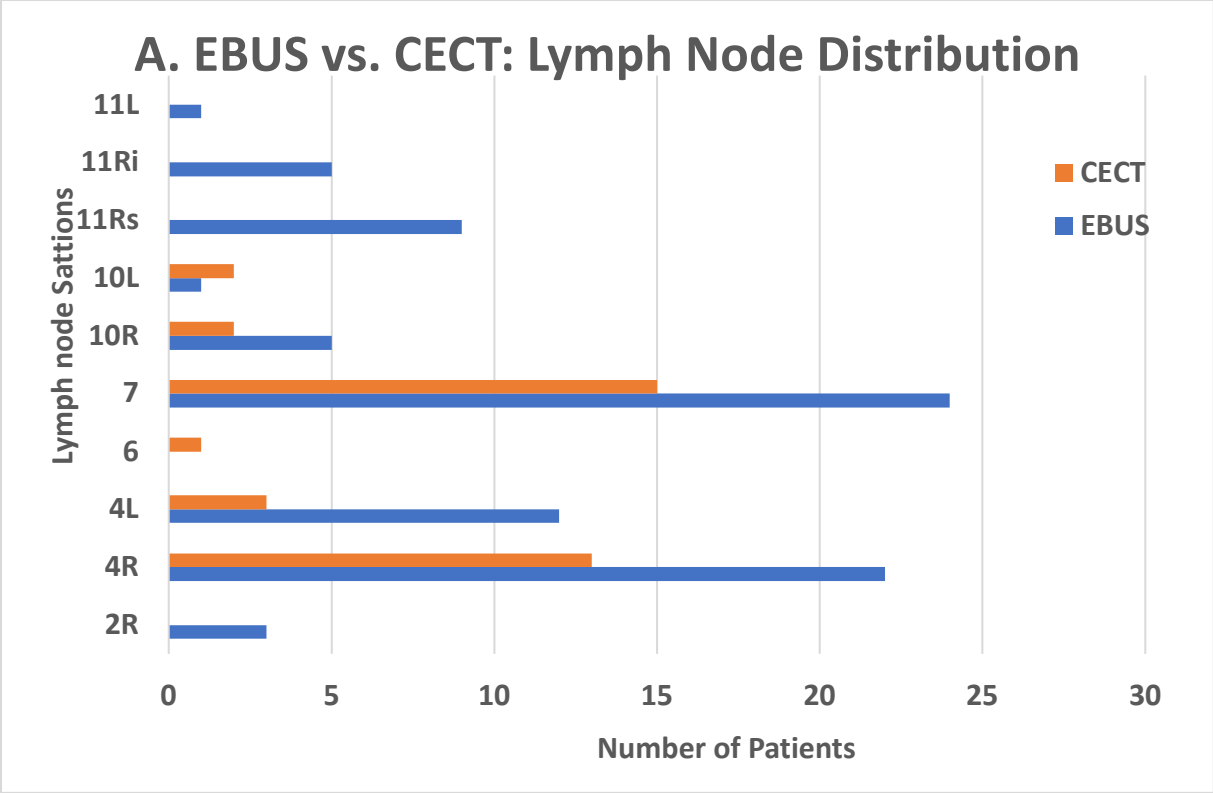
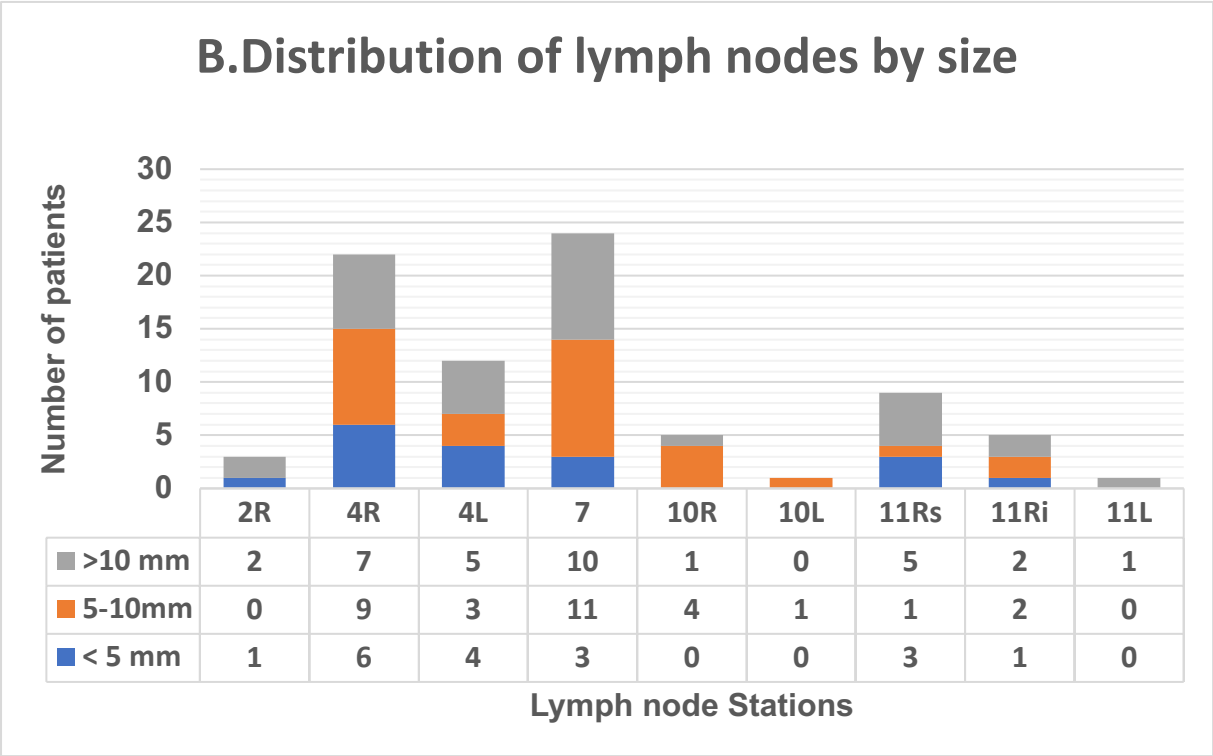
Table 1. Patient baseline data and CECT findings.

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)

Table 2. Frequency of lymph nodes EBUS sonographic features(n-82)

EBUS features	**Malignant features n (%)**	**Benign features n (%)**
Size	>10 mm 33(40 %)	<10mm 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%)





	2R	4R	4L	7	10R	10L	11Rs	11Ri	11L
>10 mm	2	7	5	10	1	0	5	2	1
5-10mm	0	9	3	11	4	1	1	2	0
< 5 mm	1	6	4	3	0	0	3	1	0

Figure 1. A) Comparison of frequency of distribution of lymph nodes at various lymph node stations in CECT and EBUS. B) Distribution of lymph nodes by size involving various lymph node stations in EBUS.

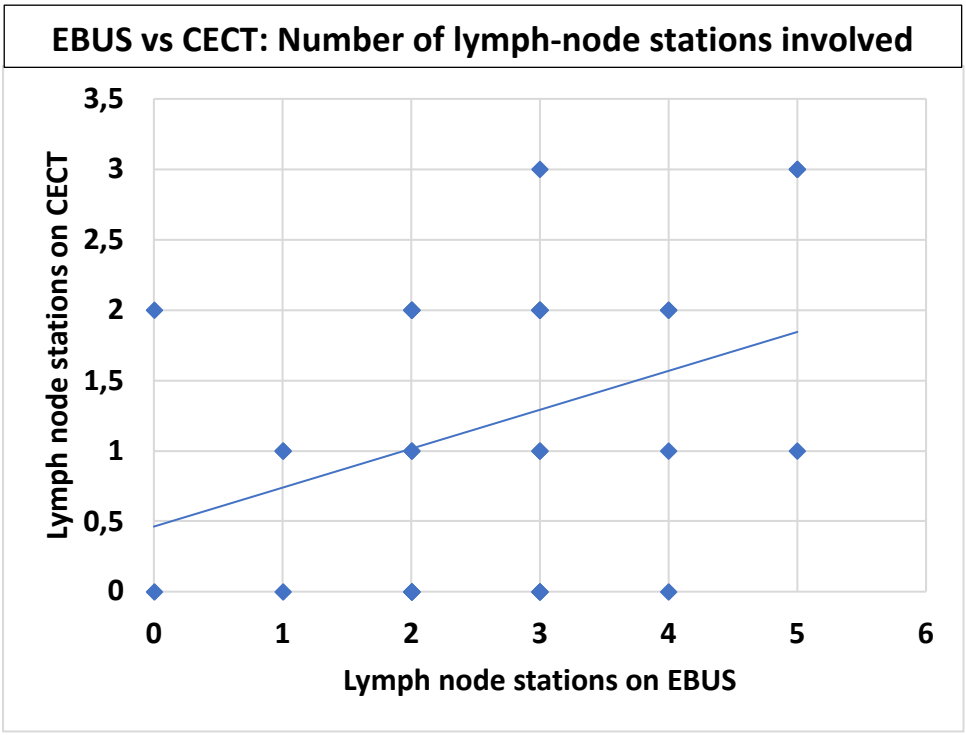
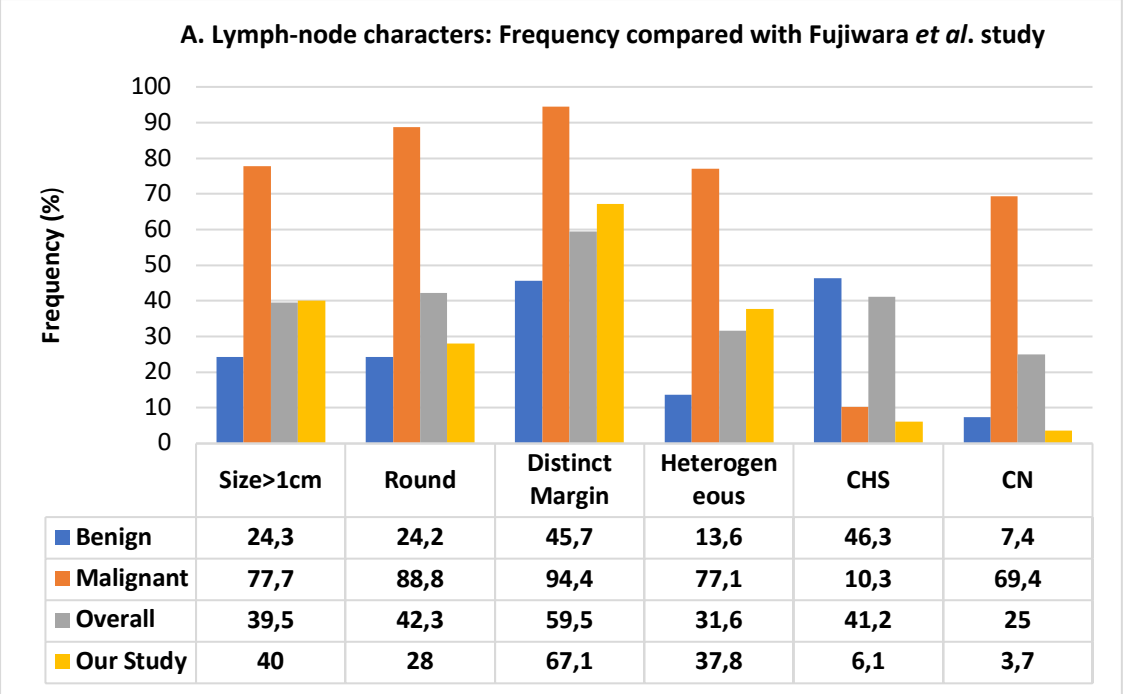
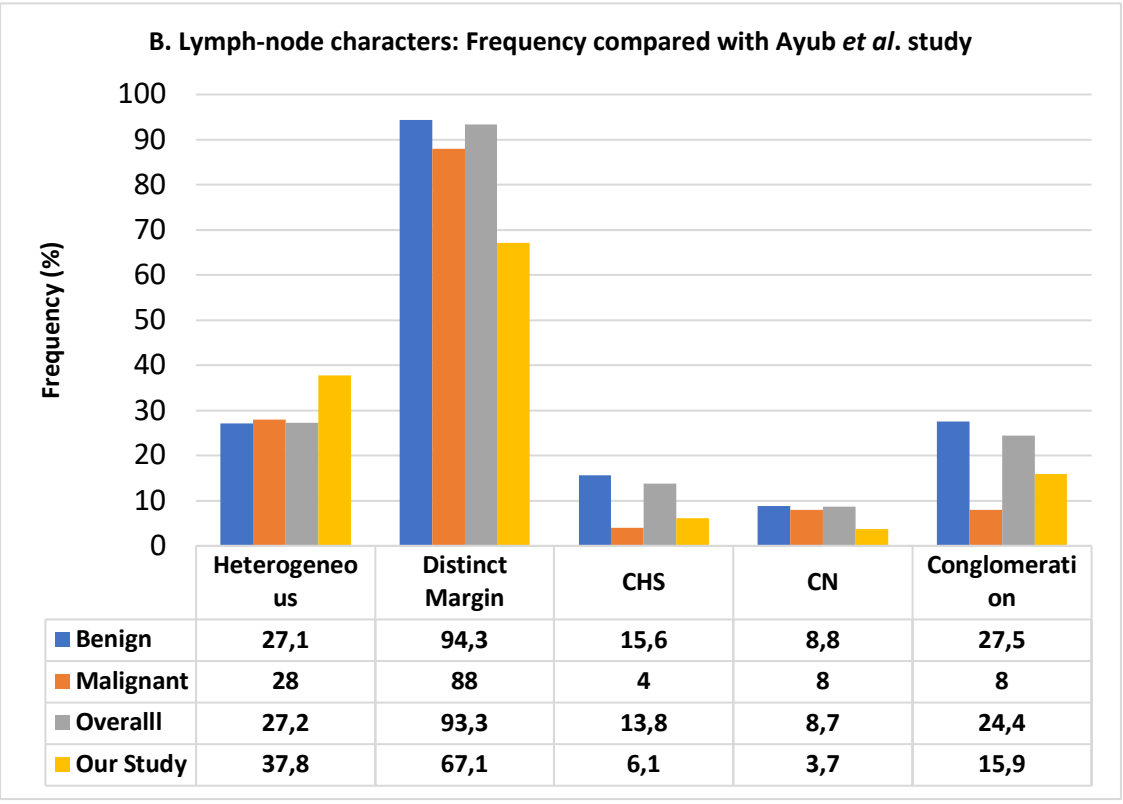


Figure 2. Spearman rank correlation test between CECT and EBUS showing significant but weak correlation of lymph node stations involved.



	Size>1cm	Round	Distinct Margin	Heterogeneous	CHS	CN
Benign	24,3	24,2	45,7	13,6	46,3	7,4
Malignant	77,7	88,8	94,4	77,1	10,3	69,4
Overall	39,5	42,3	59,5	31,6	41,2	25
Our Study	40	28	67,1	37,8	6,1	3,7



	Heterogeneous	Distinct Margin	CHS	CN	Conglomeration
Benign	27,1	94,3	15,6	8,8	27,5
Malignant	28	88	4	8	8
Overalll	27,2	93,3	13,8	8,7	24,4
Our Study	37,8	67,1	6,1	3,7	15,9

Figure 3. Comparison of frequency of lymph node features in EBUS with previous studies.