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ORIGINAL ARTICLE / ÖZGÜN MAKALE

A valuable endobronchial ultrasound scoring system predicting malignant lymph nodes

Malign lenf nodlarını öngören değerli bir endobronşiyal ultrason skorlama sistemi

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ABSTRACT

Background: This study aims to determine the sonographic criteria of lymph nodes to predict malignancy with endobronchial ultrasound.

Methods: A total of 1,987 lymph nodes of 967 patients (666 males, 301 females; mean age: 62.1±11.9 years; range, 21 to 90 years) between May 2016 and July 2020 were retrospectively analyzed. The endobronchial ultrasound images of lymph nodes were evaluated according to the following criteria: size (short axis >1 cm), shape (round or oval), margin (distinct or indistinct), coagulation necrosis sign (present or absent), central hilar structure (present or absent) and echogenicity (homogeneous or heterogeneous). A scoring system was developed for predicting malignancy.

Results: A total of 765 (38.5%) of the lymph nodes were malignant. In the univariate analysis, size >1 cm, round shape, distinct margin, absence of central hilar structure, presence of coagulation necrosis sign, and heterogeneity were significant predictors of malignancy (p<0.001 for all). In the multivariate analysis, the main independent predictors were heterogeneity and presence of coagulation necrosis sign (odds ratio=5.9, 95% confidence interval: 4.2-8.2 *vs*. odds ratio=3.1 95% confidence interval: 2.2-4.5, respectively). A cut-off value for endobronchial ultrasound score of ≥4 increased the malignancy risk 30 times with a sensitivity of 84.7%, and specificity of 84.5%.

Conclusion: Our study results show that endobronchial ultrasound scoring system with six criteria has a high sensitivity and specificity for predicting malignant lymph nodes.

Keywords: Endobronchial ultrasound, lymph node, malignancy, score.

ÖZ

Amaç: Bu çalışmada endobronşiyal ultrason ile malignitenin öngörülmesinde sonografik lenf nodu kriterleri belirlendi.

Çalışma planı: Mayıs 2016-Temmuz 2020 tarihleri arasında 967 hastanın (666 erkek, 301 kadın; ort. yaş: 62.1±11.9 yıl; dağılım 21-90 yıl) toplam 1987 lenf nodu retrospektif olarak incelendi. Lenf nodlarının endobronşiyal ultrason görüntüleri şu kriterlere göre değerlendirildi: boyut (>1 cm kısa eksen), şekil (yuvarlak veya oval), kenar (belirgin veya belirsiz), pıhtılaşma nekroz işareti (var veya yok), merkezi hiler yapı (var veya yok) ve ekojenite (homojen veya heterojen). Maligniteyi öngörmek için bir skorlama sistemi geliştirildi.

Bulgular: Lenf nodlarının toplam 765'i (%38.5) malign idi. Tek değişkenli analizde >1 cm boyut, yuvarlak şekil, belirgin kenar, merkezi hiler yapı yokluğu, pıhtılaşma nekroz işareti varlığı ve heterojenite malign lenf nodlarının anlamlı öngördürücüleri idi (tümü için p<0.001). Çok değişkenli analizde, başlıca bağımsız öngördürücüler heterojenite ve pıhtılaşma nekroz işareti varlığı idi (sırasıyla olasılık oranı=5.9, %95 güven aralığı: 4.2-8.2 ve olasılık oranı=3.1, %95 güven aralığı: 2.2-4.5). ≥4 endobronşiyal ultrason skorunun eşik değeri, %84.7 duyarlılık ve %84.5 özgüllük ile malignite riskini 30 kat artırdı.

Sonuç: Çalışma sonuçlarımız altı kriterden oluşan endobronşiyal ultrason skorlama sisteminin malign lenf nodlarını öngörmede yüksek duyarlılık ve özgüllüğe sahip olduğunu göstermektedir.

Anahtar sözcükler: Endobronşiyal ultrason, lenf nodu, malignite, skor.

Intrathoracic lymph node enlargements are detected in diseases such as lung cancer, extrathoracic malignancy metastasis, infections, lymphoma, granulomatous inflammation, and anthracosis.[1,2] Thoracic computed tomography (CT) and positron emission tomography (PET)-CT are two important techniques for non-invasive of mediastinal lymph nodes. For histopathological diagnosis, the first

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recommended step are usually minimally invasive endoscopic techniques.[3] Of these, endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) has increasingly become one of the most common diagnostic methods used to evaluate intrathoracic lymphadenopathies.[1,4,5] Recently, with growing evidence and clinical experience, EBUS-TBNA has become an alternative to mediastinoscopy, which is the gold-standard technique in lung cancer preoperative staging.[6] In lung cancer patients, the sensitivity and specificity of the EBUS are 93% and 95%, respectively.[7] The isolated mediastinal and/or hilar lymph node sensitivity of the EBUS-TBNA is 89.8% with a diagnostic yield of 91.6%.[8]

Several studies have shown that sonographic criteria can be used to predict malignant lymph nodes.[9-12] During EBUS, diagnostic efficiency is increased by sampling lymph nodes suspected to be malignant by the sonographic appearance of lymph nodes. In this way, unnecessary invasive procedures and biopsy repetitions can be prevented.[13] The diagnostic value of sonographic criteria in predicting malignancy of lymph nodes varies between studies. Some studies have proposed scoring systems developed with prespecified sonographic criteria.[10-15] However, there are limited data on this subject in the literature.

In the present study, we aimed to establish sonographic criteria to be used in the prediction of the malignant lymph nodes in EBUS and to develop a scoring system using these criteria.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dokuz Eylül University Faculty of Medicine, Department of Pulmonology, Interventional Bronchoscopy Unit between May 2016 and July 2020. Data of the patients were retrieved from the hospital database. Patients whose lymph nodes were >1 cm on thoracic CT or maximum standardized uptake value (SUV_{max}) >2.5 on PET-CT were included. Patients who had non-diagnostic pathological results, previous chemotherapy history, and unavailable ultrasonographic images were excluded from the study. A total of 1,067 patients who underwent EBUS-TBNA and 2,135 lymph nodes biopsied were evaluated. Of them, 100 patients were excluded from the study. The pathology results were non-diagnostic in 45 patients, digitally recorded ultrasonographic images could not be reached in 38 patients, and 17 patients received chemotherapy before the procedure and all were excluded from the study. Finally, 1,987 lymph nodes of 967 patients (666 males, 301 females; mean age: 62.1±11.9 years; range, 21 to 90 years) were included in the study (Figure 1).

Data including age, sex, and EBUS-TBNA indications were recorded. In addition to thoracic CT and PET-CT findings of lymph nodes, the lymph node

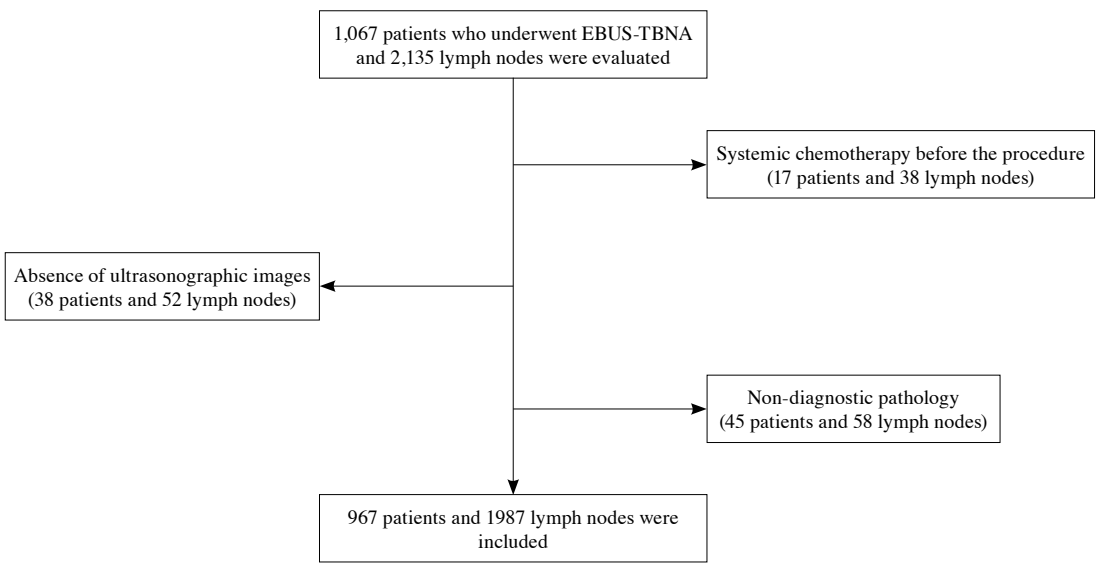

Figure 1. Study flowchart.
EBUS: Endobronchial ultrasound; TBNA: Transbronchial needle aspiration.

stations were collected according to the International Association for the Study of Lung Cancer (IASLC) map.[16]

EBUS-TBNA procedure

In our clinic, EBUS-TBNA procedures were performed by a single experienced interventional pulmonologist. Before EBUS-TBNA, the patients suitable for sedation were identified by an anesthesiologist. All procedures were performed with intravenous midazolam and fentanyl in the presence of an anesthesiologist in the bronchoscopy unit. During the procedure, heart rate, pulse oxygen saturation, and blood pressure were monitored in all patients, and oxygen support was initiated depending on pulse oxygen saturation.

The EBUS system consists of a flexible convex-probe ultrasonic-puncture bronchoscope with a linear scanning transducer at a frequency of 7.5 MHz (EB-530US, SU-8000 Endoscopic Ultrasound System, Fujifilm, Tokyo, Japan). The TBNA was obtained by a 22-gauge standard needle (Olympus Medical Systems Corp., Tokyo, Japan). Biopsy was taken from a maximum of three stations from lymph nodes visible with EBUS. The specimens were expelled for cytology into liquid fixative, suitable for cell block preparations, and evaluated by both cytological and mycobacterial examinations. The lymph node was sampled from a minimum to a maximum of six times. The rapid on-site cytopathological examination was not possible to perform.

EBUS imaging characteristics of lymph nodes

Digitally recorded EBUS images of all lymph nodes were evaluated by two pulmonologists blindly according to the criteria determined by Fujiwara et al.[9] These sonographic criteria were as follows: size (short axis ≥1 cm or <1 cm), shape (round or oval), margin (distinct or indistinct), central hilar structure (CHS) (present or absent), coagulation necrosis sign (CNS) (present or absent) and echogenicity (homogeneous or heterogeneous). Short and long axis ratio of lymph nodes >1.5 oval or <1.5 round. Distinct margin was defined as clear visualization of >50% of the margin; otherwise, it was defined as an indistinct margin. The CHS was a linear, flat, hyperechoic area within the center of the lymph node. The CNS was a hypoechoic area without blood flow within the lymph node. Heterogeneous echogenicity presented as several hypoechoic areas within the lymph nodes.[8]

EBUS scoring system

Scoring (EBUS score; one point was given for each score) was developed with six criteria that were found to be significant for predicting malignancy. All six sonographic criteria of the lymph nodes were compared with the final pathological result of the lymph node.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.5 software (IBM Corp., Armonk, NY, USA). The Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Mann-Whitney U test was used to compare parameters that did not show normal distribution between groups, and the Student t-test was used to compare normally distributed parameters. The chi-square and Fisher exact tests were used to compare categorical data between the groups. The predictive values of EBUS criteria for the diagnosis of malignancy were calculated by univariate and multivariate logistic regression analyses. The optimal cut-off values, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and probability ratios of the scoring system created from EBUS parameters were calculated by the receiver operating characteristic (ROC) analysis according to the area under the curve (AUC) and the Youden's index. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Patients and lymph node characteristics

In this study, 967 patients and 1,987 lymph nodes were evaluated. Among the EBUS indications of the patients, 58.2% had a probable diagnosis of lung cancer, 24.3% had probable metastasis of an extrapulmonary malignancy, and 17.5% had mediastinal and hilar lymphadenopathy of unknown etiology.

A total of 781 lymph nodes were sampled from the superior mediastinal, 551 subcarinal and 655 lymph nodes from the hilar region. The number of biopsies taken during the procedure ranged from one to a maximum of six, and commonly three biopsies were taken. The diameter of the lymph nodes was similar in both thoracic CT and EBUS, and the SUV_{max} value of most of them was higher than 2.5 on PET-CT in most of the patients. The radiological and sonographic features of the lymph nodes are shown in Table 1.

The final pathological diagnosis was malignancy in 765 (38.5%) of the lymph nodes and most of them were due to lung cancer (n=594, 77.6%). Half of the biopsied lymph nodes with lung cancer were adenocarcinoma

Table 1. Radiological and sonographic features of lymph nodes (n=1,987)

	n	%	Mean±SD	Min-Max
Thorax CT diameter (mm)			19.4±10.2	5.0-50.0
PET SUV			6.4±4.2	0.0-40.2
PET SUV value				
<2.5	129	8.5		
≥2.5	1,386	9.15		
EBUS size			16.3±8.4	3.0-50.0
EBUS size				
≤1 cm	522	26.3		
>1 cm	1,465	73.7		
EBUS shape				
Oval	1,125	56.6		
Round	862	43.4		
EBUS margin				
Distinct	1,233	62.1		
Indistinct	754	37.9		
EBUS CNS				
Absent	1,402	70.6		
Present	585	29.4		
EBUS CHS				
Absent	1,526	76.8		
Present	461	23.2		
EBUS echogenicity				
Homogeneous	1,167	58.7		
Heterogeneous	820	41.3		

SD: Standard deviation; CT: Computed tomography; PET: Positron emission tomography; SUV: Standardized uptake value; EBUS: Endobronchial ultrasound; CNS: Coagulation necrosis sign; CHS: Central hilar structure.

Table 2. Pathological features of lymph nodes (n=1,987)

	n	%
Lung cancer histological subgroup		
Small cell	124	20.9
Squamous cell	104	17.5
Adenocarcinoma	301	50.7
Neuroendocrine	12	2.0
Other	53	8.9
Extrapulmonary malignancy		
Head-neck	7	6.9
Breast	39	38.6
Lymphoma	8	7.9
Colorectal	18	17.9
Urogenital	23	22.8
Other	6	5.9
Benign diagnosis		
Reactive	929	76.2
Granulomatous inflammation	75	6.2
Anthracosis	215	17.6

(n=301, 50.7%). A total of 101 (13.2%) lymph nodes were extrapulmonary malignancy metastases. Breast (n=39, 38.6%) and urogenital cancer (n=23, 22.8%) were the most common metastatic cancers among sampled lymph nodes. The pathological diagnoses of the lymph nodes are presented in Table 2.

The mycobacterial examination analyzed from the suspected samples (999 lymph nodes) revealed *Mycobacterium tuberculosis* in 21 (2.1%) lymph node samples and *Mycobacterium kansasii* grew in two lymph node samples.

Complications occurred in 44 patients (4.6%) during the procedure. Desaturation (pulse oxygen saturation <92%; n=19, 43.2%) and minor bleeding (n=18, 40.9%) were the most common complications. As serious complications, massive bleeding occurred in three patients (6.8%), arrhythmia in one patient, pneumomediastinum in one patient, and cardiac arrest during the procedure in two patients. There were no deaths during the procedure.

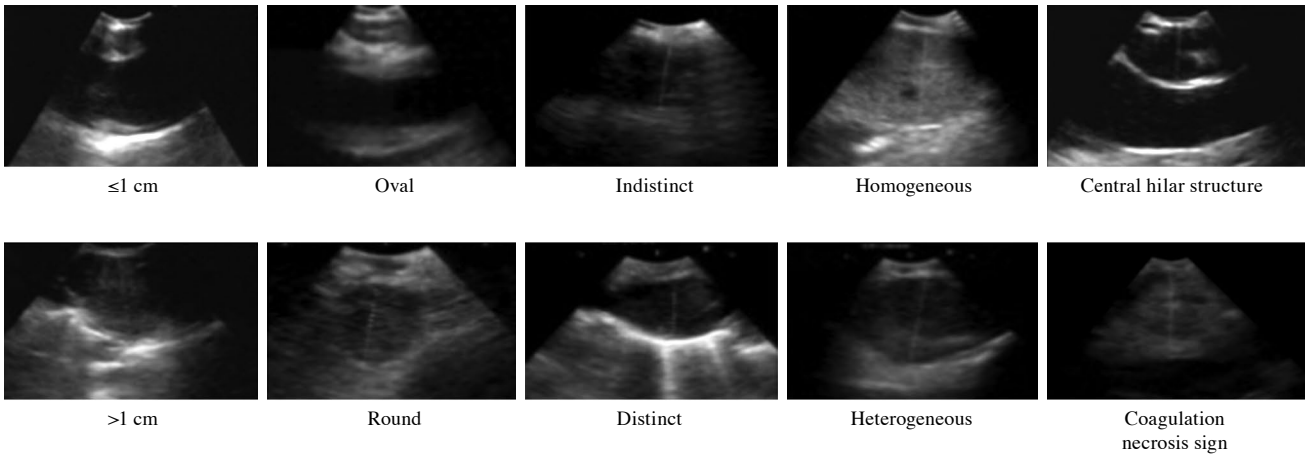

Figure 2. The ultrasound images of lymph nodes.

There was no significant difference in regions and complications between malignant and benign lymph nodes (p=0.103 and p=0.797, respectively). However, thoracic CT size, PET-CT SUV_{max} values, EBUS size, and EBUS score values were higher in malignant lymph nodes (p<0.001 for all).

EBUS sonographic features

Sonographic features of lymph nodes (size >1 cm, round shape, distinct margin, absence of CHS, presence of CNS, heterogeneous echogenicity) were found to be statistically significant in predicting malignancy (p<0.001 for all parameters). The ultrasound images of these findings are in Figure 2.

In the univariate analysis, the parameter with the highest sensitivity (95.8%) was the absence of CHS, and the highest specificity (84.9%) was heterogeneity. Sensitivity, specificity, PPV, and NPV values of EBUS sonographic parameters are shown in Table 3.

Lymph nodes showing features of heterogeneity, presence of CNS, and absence of CHS parameters were 26.8 (95% CI: 20.4-35.2) times higher risk for malignancy. The sensitivity, specificity, PPV, and NPV values of the combination of these parameters were 65%, 93.5%, 86.3%, and 81%, respectively.

In the ROC curve analysis for the median value of the EBUS size in predicting malignant lymph nodes, the cut-off value was determined as 13.5 mm. The sensitivity of this value was 77%, specificity was 60.2%, PPV was 54.8%, and NPV was 80.7%. (AUC: 0.765, p<0.001; 95% CI: 4.134-6.213) (Figure 3).

Table 3. Malignancy prediction values of EBUS parameters

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Size				
≤1 cm *vs*. >1 cm	90.2	36.6	47.1	85.6
Shape				
Oval *vs*. round	75.9	77.0	67.4	83.6
Margin				
Indistinct *vs*. distinct	83.5	51.4	51.8	83.3
Coagulation necrosis sign				
Absent *vs*. present	85.6	81.2	65.5	93.1
Central hilar structure				
Present *vs*. absent	95.8	35.1	48.1	93.0
Echogenicity				
Homogeneous *vs*. heterogeneous	83.2	84.9	77.6	88.9

EBUS: Endobronchial ultrasound; PPV: Positive predictive value; NPV: Negative predictive value.

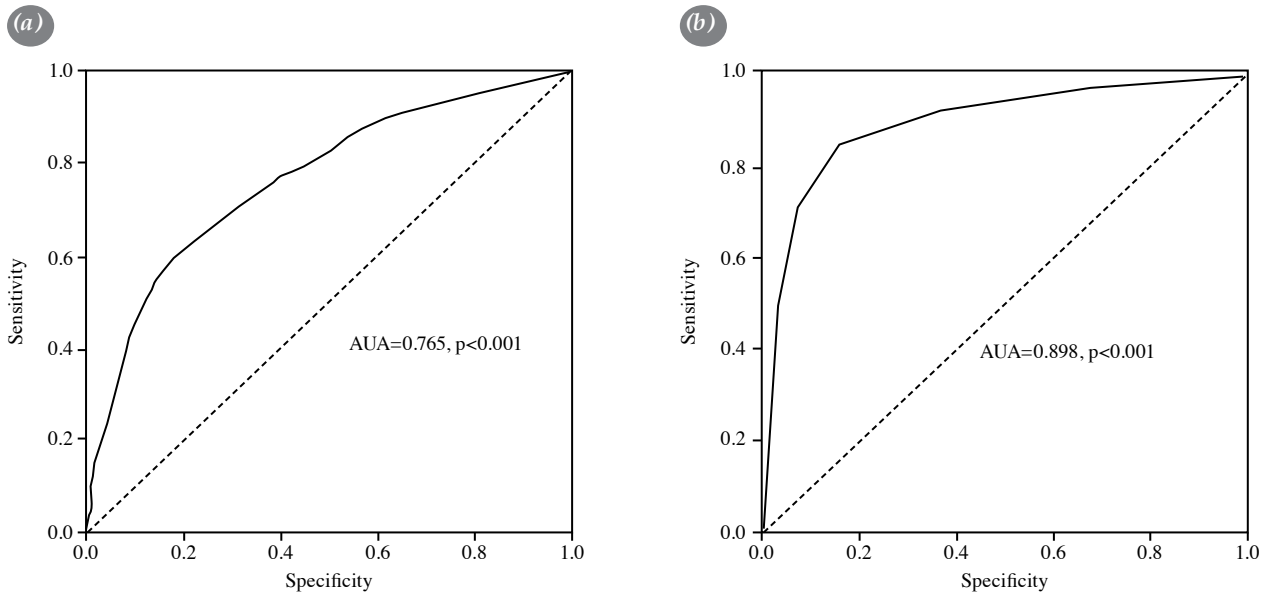

Figure 3. (a) Cut-off value for EBUS lymph node size in predicting malignancy. **(b)** Cut-off value for EBUS score in predicting malignancy.
EBUS: Endobronchial ultrasound.

Table 4. Univariate and multivariate analysis of EBUS parameters

	Univariate analysis			Multivariate analysis*		
EBUS parameters	OR	95% CI	*p*	OR	95% CI	*p*
Size						
≤1 cm *vs*. >1 cm	5.06	4.13-6.21	<0.001	1.75	1.23-2.48	0.002
Shape						
Oval *vs*. round	10.57	8.54-13.08	<0.001	2.41	1.81-3.21	<0.001
Margin						
Indistinct *vs*. distinct	5.36	4.29-6.69	<0.001	2.34	1.73-3.10	<0.001
Coagulation necrosis sign						
Absent *vs*. present	25.71	19.68-35.58	<0.001	3.12	2.17-4.48	<0.001
Central hilar structure						
Present *vs*. absent	12.39	8.53-17.99	<0.001	2.52	1.65-3.86	<0.001
Echogenicity						
Homogeneous *vs*. heterogeneous	27.81	21.73-35.56	<0.001	5.90	4.23-8.24	<0.001

EBUS: Endobronchial ultrasound; OR: Odds ratio; CI: Confidence interval.

In the ROC curve analysis performed for the EBUS scoring system in predicting malignancy, the cut-off value was found to be 3.5. The sensitivity of this value was 84.7%, specificity was 84.5%, PPV was 77.3%, and NPV was 89.3% (AUC: 0.898, p<0.001; 95% CI: 23.419-38.642). The malignancy risk of those with an EBUS score of ≥4 was found to be 30.0 (range, 23.4 to 38.6) times higher than those with an EBUS score of ≤3, and the scoring was found to be statistically significant in predicting malignancy (Figure 3).

In the multivariate regression analysis, heterogeneity of the lymph node and the presence of CNS in the lymph node were determined as the significant factors in predicting malignancy (odds ratio [OR]=5.9 95% CI: 4.2-8.2 *vs*. OR=3.1 95% CI: 2.2-4.5, respectively). Multivariate analysis values of the EBUS parameters are presented in Table 4.

DISCUSSION

Endobronchial ultrasound is a minimally invasive bronchoscopic technique used for the evaluation of intrathoracic lymphadenopathy and lesions of the airway wall.[17] Using the EBUS-TBNA, ultrasonographic features can be used in predicting malignancy in mediastinal lymph nodes.[18] This study was conducted to establish a sonographic scoring system to predict malignant lymph nodes.

In this study population, elderly male patients were mostly similar to other studies.[9,10] Among the patients who were found to be malignant, adenocarcinoma was the most common neoplasm. According to epidemiological data, lung adenocarcinoma is the most common primary lung cancer.[19] Consistent with these data, adenocarcinoma was diagnosed more frequently in our patients.

In the literature, there are different opinions about the relationship between lymph node size and malignancy. Shafiek et al.[15] performed a retrospective analysis of 208 lymph nodes in 141 patients and demonstrated that lymph nodes >1 cm were significant predictors of malignancy. On the other hand, Fujiwara et al.[9] reported that >1-cm lymph nodes were not predictors of malignancy. In our study, lymph nodes >1 cm were significant predictors of malignancy ($p<0.001$), and the most optimal cut-off value for the diameter was 13.5 mm. These different results show that lymph node size alone is insufficient in predicting malignancy. Also, patient characteristics and SUV_{max} of lymph node can be different in these studies.

Hylton et al.[13] reported in a systematic review by including 13 studies that the most sensitive parameter in predicting malignancy was the absence of CHS at 94.2%. All sonographic parameters (Doppler findings except) were found to predict malignancy in the meta-analysis of 29 studies by Agrawal et al.[20] In this study, CHS had the highest sensitivity and CNS had the highest specificity in the prediction of malignancy (OR=0.91, 95% CI: 0.90-0.92 *vs*. OR=0.93, 95% CI: 0.92-0.94, respectively). We found that all parameters were significant in malignancy. The highest sensitivity (95.8%) was CHS, similar to the literature, and the highest specificity was echogenicity (84.9%) in our study.

During the EBUS procedure, it is recommended to use a combination of different sonographic criteria.[20] The presence of >1 cm, round, distinct margin, and heterogeneous features in the lymph node had a sensitivity of 46.3%, specificity of 95.3% in the study by Lin et al.[12] Hylton et al.[14] also reported that the malignancy increased by 15 times in the presence of three of the four criteria (>1 cm, distinct margin, absence of CHS, and presence of CNS). We developed the EBUS score in our study, and the risk of malignancy was found to be 30.0 times higher in the lymph node with ≥4 parameters (>1 cm, round shape, distinct margin, absence of CHS, and presence of CNS, heterogeneity). This study included the highest number of patients and number of lymph nodes and the EBUS scoring system we developed in our study was found to have a high sensitivity and specificity (84.7% and 84.5%, respectively) compared to the other studies on this topic.

The most commonly reported complications related to EBUS are pneumothorax, infections, and respiratory complications. In a meta-analysis of 190 studies, the major problems after EBUS-TBNA (infection, pneumothorax, and perforation) were observed in 0.05% of cases, and mortality was not documented.[21] Among our complication rates, there were mostly minor complications. These findings suggest that EBUS is a safe procedure with low complication rates when performed by an experienced team. We also believe that the complication rates may vary according to the patient-reported outcomes.

The main limitations to our study are its single-center and retrospective design. In addition, comorbidities and smoking history of the patients were unable to be evaluated. The quality of ultrasound images varied for each procedure. Different ultrasonographic criteria such as Doppler findings, vascularization, calcification, conglomeration, and elastography were unable to be evaluated, either.

In conclusion, sonographic features with endobronchial ultrasound in mediastinal lymph nodes are a valuable method of predicting malignancy with a high sensitivity and specificity. The main predictors of malignancy were heterogeneity and the presence of coagulation necrosis sign in our study. Based on these findings, the use of the endobronchial ultrasound score in the prediction of malignancy seems to increase diagnostic efficiency and reduce unnecessary invasive procedures. Further large-scale studies are needed to validate and demonstrate the efficiency of the sonographic scoring system for predicting malignancy in endobronchial ultrasound transbronchial needle aspiration.

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Faculty of Medicine Ethics Committee (date: 17.08.2020, no: 2020/19-28). The

study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea, design, data collection, literature review, writing the article: N.G.; Control/supervision, writing article, analysis: K.C.T.; Analysis, data collection: D.G.

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