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The value of endobronchial ultrasound-guided transbronchial needle aspiration, 18-fluorodeoxyglucose positron emission tomography/computed tomography, and ultrasonography imaging techniques in the diagnosis of mediastinal and/or hilar malignant, anthracotic, and other benign lymph nodes

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Abstract

Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a simple, reliable, minimally invasive and effective procedure. However, a surgical technique may be required, if the results are negative. Therefore, there is a need for new studies to increase the diagnostic value of EBUS-TBNA and provide additional information to guide the biopsy in performing the procedure. Here, we aimed to investigate the diagnostic value of EBUS-TBNA and 18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) in diagnosis of hilar and/or mediastinal lymph nodes (LNs). It was also aimed to determine the contributions of real-time ultrasonography (USG) images of LNs to distinguishing between the malignant and benign LNs during EBUS-TBNA, and in the diagnosis of anthracotic LNs.

Material and Method: In the retrospective study including 545 patients, 1068 LNs were sampled by EBUS-TBNA between January 2015 and February 2020. EBUS-TBNA, 18-FDG PET/CT and images of USG were investigated in the diagnosis of mediastinal and/or hilar malignant, anthracotic and other benign LNs.

Results: The sensitivity, specificity, positive predictive value and negative predictive value of EBUS-TBNA were found as 79.5, 98.1, 89.5, and 91.7%, respectively. Mean maximum standardized uptake value (SUVmax) values of 18F-FDG PET/CT were 6.31±4.3 in anthracotic LNs and 5.07 ± 2.53 in reactive LNs. Also, mean SUVmax of malignant LNs was 11.02 ± 7.30 and significantly higher than that of benign LNs. In differentiation of malignant-benign tumors, considering the cut off value of 18F-FDG PET/CT SUVmax as 2.72, the sensitivity and specificity was 99.3 and 11.7%, but given the cut off value as 6.48, the sensitivity, specificity, positive predictive value and negative predictive value was found as 76.5, 64, 20.49, and 78.38% for benign LNs, respectively. Compared LNs as to internal structure and contour features, malignant LNs had most often irregular contours and heterogeneous density. Anthracotic, reactive and other benign LNs were most frequently observed as regular contours and homogeneous density. The difference between malignant and benign LNs was significant.

Conclusion: EBUS can contribute to the differential diagnosis of malignant, anthracotic and other benign LNs. Such contributions can guide clinician bronchoscopists during EBUS-TBNA. The triple modality of EBUS-TBNA, 18FDG PET/CT, and USG may increase the diagnostic value in hilar and mediastinal lymphadenopathies.

Abbreviations: 18 FDG-PET/CT = 18-fluorodeoxyglucose positron emission tomography/computed tomography, CT = computerized tomography, EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration, EUS = endo-esophageal ultrasonography, FNAB = fine needle aspiration biopsy, LAPs = lymphadenopathies, LNs = lymph nodes, NPV =

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negative predictive value, NSCLC = non-small cell lung cancer, PPV = positive predictive value, ROC = receiver operating characteristic, SUVmax = maximum standardized uptake value, TB = tuberculosis, USG = ultrasonography.

Keywords: 18-fluorodeoxyglucose positron emission tomography/computed tomography, anthracosis, endobronchial ultrasound-guided transbronchial needle aspiration, lymph node, mediastinal lymphadenopathy, mediastinal ultrasonography

1. Introduction

Transbronchial needle aspiration, accompanied by endobronchial ultrasonography (EBUS-TBNA), has been an important method frequently used both in the diagnosis and staging of mediastinal lesions with suspected malignancy and in the initial investigation of the diagnosis of benign lesions.[1] In cancer patients with mediastinal lymphadenopathies (LAPs), the samples of lymph nodes (LNs) are required to be obtained before deciding the treatment. EBUS-TBNA has been recommended in the cases of mediastinal lymphadenopathy under the international guidelines[2,3] and become the standard diagnostic procedure.[4] Metastasis of mediastinal LNs is one of the most important determinants in deciding the treatment protocol and prognosis in the patients with pulmonary or extrapulmonary malignancies.[5,6] Mediastinal and hilar LAPs do not always result from cancer, but granulomatous diseases and pneumoconiosis may also be the causes of mediastinal or hilar LAPs.[7] In addition, such benign diseases as tuberculosis (TB) or sarcoidosis accompanying cancer can also lead to mediastinal LAPs.[5,6] As another benign condition, anthracosis is a type of pneumoconiosis caused by coal dust, air pollution as one of other environmental factors, smoking and the smoke from biomass fuels commonly used for cooking in rural areas. Anthracosis brings about some changes not only in the lung parenchyma but also in LNs.[8] Additionally, anthracosis mimicking malignancy may also cause false positivity in 18-fluorodeoxyglucose positron emission tomography in computed tomography (18F-FDG PET/CT).[8,9] Such a false positive finding in anthracosis may mislead the clinicians in the mediastinal staging of lung cancer.[10] EBUS-TBNA is a simple, reliable, minimally invasive, and effective procedure. However, since EBUS-TBNA is likely to result in inadequate diagnosis, the results are required to be confirmed through an invasive technique, if the findings are negative.

Although still remaining the gold standard in the evaluation of the mediastinum, mediastinoscopy requires general anesthesia and is associated with higher morbidity and mortality, as well as being unavailable for the evaluation of hilar LNs.[11] For this reason, further studies are needed to increase the diagnostic value of EBUS-TBNA, to guide how many biopsy samples should be taken from which LNs by providing additional information in performing the procedure, and to improve its use. Other imaging methods, including thorax computerized tomography (CT) and 18F-FDG PET/CT, are still available for the detection and differential diagnosis of mediastinal and hilar lesions.[12] 18F-FDG PET/CT is the most widely used noninvasive imaging technique for the clinical staging of lung cancer.[13] However, such modalities are considered to be inadequate in clinical decision making due to not allowing pathological confirmation.[12] In addition, relatively high FDG uptake of anthracotic LNs makes it difficult to differentiate LNs with 18F-FDG PET/CT. Recent studies have revealed that the diagnostic accuracy of FDG-PET is quite low and similar to that obtained on CT in those suffering from pneumoconiosis.[8] Therefore, there is still a need for noninvasive methods to provide additional information for mediastinal and hilar LAPs. The features of endobronchial ultrasound (EBUS) are useful in distinguishing between benign and malignant LNs, but the data on anthracosis obtained frequently thanks to the enlargement of mediastinal LNs still remain limited.[14] In the present study, we aimed to investigate the diagnostic value of EBUS-TBNA and 18F-FDG PET/CT in the diagnosis of hilar and/or mediastinal LNs. We also determined the contributions of the real-time ultrasonography (USG) images of mediastinal and hiler LAPs detected as a novelty during EBUS-TBNA to distinguishing between malignant and benign LAPs, and to both the diagnosis and differential diagnosis of anthracotic LNs. We considered that as an inexpensive and easily available method including no radiation, using endobronchial USG in differenting between malignant, anthracotic and other benign LNs may successfully provide significant information in guiding clinician bronchoscopists during EBUS-TBNA. So, the biopsies performed in light of this information may increase the diagnostic value of EBUS-TBNA.

2. Material and method

2.1. Patients

The present study was carried out retrospectively in 545 patients. The sampling was achieved with EBUS-TBNA in a university hospital between 2015 and February 2020. This study was conducted in accordance with the human rights declaration of Helsinki and later amendments, and the study protocol was approved by the local ethics committee (Registration no: 2020/2469). A total of 567 patients were evaluated with EBUS-TBNA for the diagnosis and staging of primary lung cancer and extrapulmonary malignancies, as well as other ailments, such as sarcoidosis, anthracosis, TB and lymphadenitis. From the hospital recording system, first, the patients' epicrisis files, the history obtained on admission, the findings of pathology, the reports of radiology and nuclear medicine imaging, and the information from bronchoscopy unit archive were scanned. Then, such features as demographic data, primary malignancy sites, highest maximum standardized uptake value (SUVmax) of 18F-FDG PET/CT, the images and reports of EBUS, aspirated LN stations, and the histopathological and definitive diagnoses were recorded. Twenty-two patients were excluded from the study due to the shortages in pathological diagnosis and follow-ups. Informed consent was obtained from all participants for the procedures and use of medical records prior to EBUS performed in our department.

2.2. Radiological assessment

The indications of EBUS-TBNA in the patients registered were the existence of LNs with short axis in diameter of >10 mm[15] in the mediastinal and/or hilar region in thorax CT, and/or positive 18-FDG involvement in PET-CT. The scannings of PET-CT were

performed in the staging of those with suspected and present malignancy. If an increase was defined in the metabolic activity of SUVmax >2.5 in PET-CT reports, FDG PET-CT was considered to be positive.

2.3. EBUS-TBNA procedure

All EBUS-TBNA procedures were performed by three chest diseases specialists/bronchoscopists. Each procedure was performed by two bronchoscopists working together. EBUS-TBNA was performed orally in the supine position with transbronchial ultrasonography (TBUS) bronchoscopy (Convex Probe EBUS; BF-UC 160F-OL8; Olympus Medical Systems, Tokyo, Japan) under local anesthesia with oral lidocaine and *iv* midazolam for conscious sedation. During the procedures, heart rate and oxygen saturation of all patients were monitored. By examining thorax CT and, if any, PET CT images before TBNA procedure, all mediastinal and hilar lymph node stations to be accessed through EBUS were investigated. The lymph node stations were determined under the international lymph node map on the proposals of the International Association for the Study o Lung Cancer (IASLC).[16] Tissue samples were obtained from each target node station at least twice with a 21–22-gauge special needle (NA-201SX-4022, Olympus or CDEBN03, Clinodevice). The needle was moved back and forth 30–40 times in LNs to obtain tissue sample. The biopsy material obtained in the needle was pushed with the guide and put in a container with 10% formalin. Then, the aspirate in the 10 to 20 mL syringe and needle was placed by spraying onto at least 3 glass slides. The biopsy material obtained for the comparison of mycobacterial concentrations and cultures in the required patients was immediately delivered to the microbiology laboratory. If no tissue samples were obtained during the first 2 aspirations, the aspiration from LNs was performed 3 or more times until the adequate tissue sample was obtained. For the required patients, oxygen support was given during the procedure, and all patients were closely monitored in terms of the complications, such as oxygen desaturation, arrhythmia, hemorrhage, pneumothorax and pneumomediastinum during and 30 minutes after the procedure.

2.4. Appearance of EBUS

When the records of images of LNs performed with EBUS in our archive reports were assessed, LNs were seen to be defined as four different images by the chest diseases specialist/bronchoscopist, and the images were as follows:

(1) LNs with regular contours and homogeneous density,
(2) Those with regular contours and heterogeneous density,
(3) Those with irregular contours and homogeneous density and
(4) Those with irregular contours and heterogeneous density.

Therefore, LNs were divided into 4 groups and recorded.

2.5. Pathological investigation

The aspirates were put into 10% formalin to obtain a cell block for histopathological examination. The remaining aspirates were placed on at least three glass slides, dried with air, fixed immediately with 96% alcohol and stained with hematoxylin eosin. We had no opportunity of rapid cytological examination in situ. Also, all histopathological examinations were performed by the same experienced histopathologist.

2.6. Mycobacterial investigation

The samples of fine needle aspiration biopsy (FNAB) taken from the patients and kept in sterilized containers were immediately transferred to the microbiology laboratory. In the laboratory, the samples were suspended and vortexed in a medium containing 1 mL of Middlebrook 7H9. The suspended samples were then digested and decontaminated using a commercial decontamination kit (Mycoprosaf, Salubris AS, Istanbul, Turkey). Each processed sample was evaluated for acid-resistant bacillus. The investigation of mycobacterial concentrations and cultures was performed on MGIT 960 system (BD Biosciences, Sparks, MD, USA) and Löwenstein-Jensen medium according to the manufacturer's manual.

2.7. Final diagnosis

In order to create the malignancy, when the material aspirated with EBUS-TBNA contained malignant cells, the sample was considered to be malignant. However, sarcoidosis was diagnosed with the demonstration of epiteloid cell granulomas not showing caseification in LNs through the histopathological examination and the exclusion of other causes leading to granulomatous inflammation, as well as radiological and clinical findings.[17] The diagnosis of TB was performed by showing the caseified granulomatous inflammation histopathologically or positive acid-resistant bacillus or production of M. tuberculosis in culture microbiologically. In defining anthracotic LNs, however, a LN was considered to be anthracotic LN if the compact anthracotic pigments were present in the microscopic examination of the aspirate. Considering reactive LNs, a LN was considered reactive upon the presence of lymphocytes, macrophages and immunoblasts, and in the absence of malignant cells, granulomatous inflammation and compact anthracotic pigments in the microscopic examination of the aspirates by pathologists.

2.8. Follow-up procedure

When the pathological diagnosis was incompatible with our clinical and radiological prediagnostic criteria, EBUS-TBNA was repeated. EBUS-TBNA was performed twice in 42 patients and three times in eight patients. For the suspected patients due to clinical and radiological signs, advanced invasive diagnostic methods such as mediastinoscopy (n=48) or thoracotomy (n=12) were utilized. In case of the suspicion of low malignancy, LNs were followed-up clinically and radiologically for at least one year.

2.9. Descriptions of false negativity and true negativity

On condition that the sampling of LNs was reported as malignancy through mediastinoscopy or thoracotomy, or if the diameter of LNs or the metabolic activity was increased in PET-CT during the follow-ups, EBUS-TBNA was considered to be "false negative". Even so, if the sampling of LNs by mediastinoscopy or thoracotomy confirmed anthracosis or other benign diagnoses or showed no enlargement or increased metabolic activity in LNs images on CT or PET-CT during the radiological follow-ups, EBUS-TBNA was considered "true negative".

2.10. Statistical analysis

Statistical analyzes were performed using the Statistical Package for Social Sciences v. 22.0 (SPSS Inc, Chicago, IL), and

Table 1

Demographic features, sampled lymph node stations, numbers of patients and complications.

	Mean	Min-Max
Age (yr)	**59.83 ± 13.75**	**18–88**
Gender (n) (%)	Men	Women
	305 (%56)	240 (%44)
Lymph node stations (n)	2R	31
	2L	3
	4R	265
	4L	55
	7	372
	10R	49
	10L	12
	11Rs	88
	11Ri	64
	11L	123
	12R	5
	12L	1
	Total	1068
Complications (n) (%)	Hemorrhage 4 (0.73%)	
	Desaturation 3 (0.55%)	

2R = right upper paratracheal, 2L = left upper paratracheal, 4R = right lower paratracheal, 4L = left lower paratracheal, 7 = subcarinal, 10R = right hilar, 10L = left hilar, 11Rs = right interlober superior, 11Ri = right interlober inferior, 11L = left interlober, 12R = right interlobular, 12L = left interlobular.

conformity analyzes were carried out for normal distribution. The Oneway Anova variance analysis and the post hoc Tukey analysis were utilized to compare numerical variables. In order to compare categorical data, the chi square test was used. The cut off value was determined by the receiver operating characteristic (ROC) curve. In addition, a $P < .05$ value was considered the limit of significance in all analyzes. The final diagnostic procedure based on the biopsy (EBUS-TBNA, mediastinoscopy and thoracotomy) was accepted as the gold standard for the specificity, sensitivity, and other parameters.

3. Results

Of 545 patients, 305 (56%) and 240 (44%) were male and female, and the average age was found as 59.83 ± 13.75 (min-max: 18–88). A total of 1068 samples were obtained from 12 LNs stations.

The most common pathology of LNs observed among the findings of EBUS-TBNA was detected as anthracotic LNs (n = 202, 37.1%), followed by metastasis of lung cancer LNs (n = 111, 20.3%), reactive LNs (n = 97, 17.8%) and sarcoidosis (n = 95, 17.4%). In addition, the number and rates of metastasis or involvements in other organs were observed as follows: Extrapulmonary malignancy (n = 17, 3.1%), breast carcinoma metastasis (n = 5, 0.9%), renal cell carcinoma metastasis (n = 3, 0.6%), colon carcinoma metastasis (n = 2, 0.4%), chondrosarcoma metastasis (n = 2, 0.4%), prostate carcinoma metastasis (n = 2, 0.4%), leukemia (n = 2, 0.4%) and lymphoma (n = 1, 0.2%) (Table 1). The total number of malignant LNs was also detected as 128 (23.4%).

In the definitive diagnosis, 11 patients diagnosed with anthracotic LNs through EBUS-TBNA were excluded out of anthracotic LNs group due to detecting malignancies with mediastinoscopy and thoracotomy. The diagnosis of 191 (35%) patients was determined to be only anthracotic LNs. While the number of reactive LNs fell to 73, different diagnoses were defined in 23 patients, including malignancy and sarcoidosis.

While performing the definitive diagnosis, the number of total lung cancers and extrapulmonary malignancies were determined as 134 (24.5%) and 27 (4.9%) respectively, and so the total number of malignancies reached 161 (29.5%) (Table 2). In the final diagnosis, mean age rates of the patients with malignant and benign characteristics were found as 61.83 ± 12.09 and 59 ±

Table 2

Endobronchial ultrasound-guided transbronchial needle aspiration and pathology outcomes of final diagnosis.

EBUS-TBNA Pathology	Patients (n)		Percent (%)		Pathology of Final Diagnosis	Patients (n)		Percent (%)	
Anthracotic LNs	**202**		**37.1**		**Anthracotic LNs**	**191**		**35**	
Squamous cell carcinoma	36	111	6.6	20.3	Squamous cell carcinoma	41	134	7.5	24.7
Adenocarcinoma	32		5.9		Adenocarcinoma	39		7.2	
Small cell carcinoma	23		4.2		Small cell carcinoma	25		4.6	
Non-small cell carcinoma	10		1.8		Non-small cell carcinoma	15		2.8	
Neuroendocrine tumor	7		1.3		Neuroendocrine tumor	8		1.5	
Sarcomatoid carcinoma	3		0.6		Sarcomatoid carcinoma	6		1.1	
Reactive lymph node	97		17.8		Reactive lymph node	73		13.4	
Sarcoidosis	95		17.4		Sarcoidosis	109		20	
Breast carcinoma metastasis	5	17	0.9	3.1	Breast carcinoma metastasis	5	27	0.9	4.9
Colon carcinoma metastasis	2		0.4		Colon carcinoma metastasis	2		0.4	
Renal cell carcinoma metastasis	3		0.6		Renal cell carcinoma metastasis	3		0.6	
Chondrosarcoma metastasis	2		0.4		Chondrosarcoma metastasis	2		0.4	
Prostate carcinoma metastasis	2		0.4		Prostate carcinoma metastasis	3		0.6	
Leukemia	2		0.4		Leukemia	2		0.4	
Lymphoma	1		0.2		Lymphoma	6		1.1	
Thymoma	3		0.6		Endometrium carcinoma metastasis	2		0.4	
Tuberculosis lymphadenitis	5		0.9		Nasopharyngeal carcinoma metastasis	1		0.2	
Non-diagnostic hypocellular	15		2.8		Malignant mesenchymal tumor	1		0.2	
					Tuberculosis lymphadenitis	7		1.2	
					Thymoma	3		0.6	
					Cryptogenic organized pneumonia	1		0.2	
Total	545		100		Total	545		100	

EBUS-TBNA = Endobronchial ultrasound-guided transbronchial needle aspiration, LNs = Lymph nodes.

Table 3

Comparison of 18F-FDG PET/CT SUVmax values of malignant lymph nodes metastasis with benign lymph nodes in lung cancer and non-lung cancers.

Groups of LNs	SUVmax, mean ± SD	*P* value
LNs of lung cancer (n = 112)	11.13 ± 7.20	*P* < .001
Benign LNs (n = 138)	6.48 ± 4.47	
LNs of extrapulmonary cancer (n = 20)	10.41 ± 8.01	*P* < .001
Benign LNs (n = 138)	6.48 ± 4.47	
LNs of lung cancer (n = 112)	11.13 ± 7.20	.87
LNs of extrapulmonary cancer (n = 20)	10.41 ± 8.01	

18FDG-PET/CT = fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography, LNs = lymph nodes, SD = standard deviation, SUVmax = maximum standardized uptake value.

Table 4

Comparison of SUVmax values of 18F-FDG PET/CT of malignant, anthracotic and reactive lymph nodes.

Groups of LNs	SUVmax, mean ± SD	*P* value
Malignant LNs (n = 132)	11.02 ± 7.30	*P* < .001
Anthracotic LNs (n = 94)	6.31 ± 4.3	
Malignant LNs (n = 132)	11.02 ± 7.30	*P* < .001
Reactive LNs (n = 21)	5.07 ± 2.53	
Anthracotic LNs (n = 94)	6.31 ± 4.3	.66
Reactive LNs (n = 21)	5.07 ± 2.53	

18FDG-PET/CT = Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography, LNs = lymph nodes, SD = standard deviation, SUVmax = maximum standardized uptake value.

14.32, respectively. In the differentiation between benign and malignant LNs, the sensitivity of EBUS-TBNA was determined as 79.5%, specificity as 98.1%, positive predictive value (PPV) as 89.5% and negative predictive value (NPV) as 91.7%.

Upon scanning the records in our archive, 270 images of 18F-FDG PET/CT performed within the period between one month before and after EBUS-TBNA procedure were encountered. Of 270 images, while 112 and 20 were related to metastasis of lung cancer and extrapulmonary cancer patients' LNs respectively, 138 were seen to arise from the metastasis of benign LNs patients. The average SUVmax rates of lung cancer LNs metastasis and extrapulmonary lung cancer LNs metastasis or involvements such as lymphoma and leukemia were detected as 11.13 ± 7.20 and 10.41 ± 8.01, respectively. The average SUVmax value of LNs due to benign diseases was also found to be 6.48 ± 4.47. These three groups were compared. A statistically significant difference was seen between the lung cancer and benign LNs groups ($P < .05$), and the non-lung cancer LNs metastasis and benign LNs groups ($P < .05$). However, no significant difference was detected between SUVmax values of LNs metastasis of lung and extrapulmonary cancers ($P = .87$) (Table 3).

In the differentation of malignant and benign LNs, when the cut off value of 18F-FDG PET/CT SUVmax was assumed as 2.72 according to ROC curve, the sensitivity and specificity were found to be 99.3 and 11.7%, respectively. Even so, when the cut off value of mean SUVmax for benign LNs was taken as 6.48, the rates of sensitivity, specificity, PPV and NPV were calculated as 76.5, 64, 20.49, and 78.38%, respectively.

The average age of 191 patients diagnosed with anthracotic LNs was 64.76 ± 10.29, and 99 (51.8%) and 92 (48.2%) were male and female. While the average value of 18F-FDG PET/CT SUVmax was calculated as 6.31 ± 4.3, the value for reactive LNs SUVmax was found to be 5.07 ± 2.53. SUVmax value of malignant LNs (lung cancer and extrapulmonary cancer metastasis) was 11.02 ± 7.30, and the values in both groups were significantly higher than those with benign LNs (Table 4).

The ROC curve was drawn for calculating 18F-FDG PET/CT SUVmax values in the differential diagnosis of anthracotic and malignant LNs. When the cut off value was assumed as 3, the sensitivity and specificity were calculated as 92 and 82% for the values below 3, respectively. When the differences between four groups classified according to USG images (based on contours and internal structures) of malignant and benign LNs obtained through EBUS-TBNA were investigated, it was seen that 54.6% of malignant LNs and 70.2% of benign LNs had regular contours while 45.4% of malignant LNs and 29.8% of benign LNs had irregular contours. The higher rate of irregular contours was statistically significant in malignant LNs, compared to benign LNs (Table 5).

When LNs were compared in terms of the internal structure features, 65.3% of malignant LNs and 47.5% of benign LNs were seen to be in heterogeneous density group. Even so, 52.5% of benign LNs and 34.7% of malignant LNs were found to be in homogeneous density group. The higher rate of homogeneous density in benign LNs was statistically significant (Table 6).

When the malignant and benign LNs were compared in terms of both the contours and internal structure features, it was observed that malignant LNs had the most irregular contours (40.8%) in heterogeneous density group, while benign LNs had the most regular contours (47%) in homogeneous density group. The difference between both groups was statistically significant (Table 7).

Compared the malignant, anthracotic and reactive LNs in terms of the contours, the rates of regular contours were found as 54.6% in malignant LNs, 64.8% in anthracotic LNs and 71.1% in reactive LNs. The fact that LNs with regular contours were most commonly witnessed in reactive LNs group was statistically significant (Table 9).

Table 5

Rates of malignant and benign lymph nodes according to the nature of node contours.

	LNs with regular contours (n) (%)	LNs with irregular contours (n) (%)	Total	X^2	*P* value
Patients with malignant LNs (n = 161)	159 (54.6%)	132* (45.4%)	291 (100%)	23.05	*P* < .001
Patients with benign LNs (n = 384)	546 (70.2%)	231 (29.8%)	777 (100%)		
Total number of patients (n = 545)	705	363	1068		

LNs = lymph nodes.
* The group where the difference originated

Table 6

Rates of malignant and benign lymph nodes according to the internal structure.

	LNs with homogeneous density (n) (%)	LNs with heterogeneous density (n) (%)	Total	X^2	*P* value
Patients with malignant LNs (n=161)	101 (34.7%)	190 (65.3%)	291 (100%)	26.89	$P<.001$
Patients with benign LNs (n=384)	408* (52.5%)	369 (47.5%)	777 (100%)		
Total number of patients (n=545)	509	559	1068		

LNs = lymph nodes.
* The group where the difference originated

Table 7

Rates of malignant and benign lymph nodes according to the internal structure and contours.

	Homogen with regular contours* (n) (%)	Heterogen with regular contours (n) (%)	Homogen with irregular contours (n) (%)	Heterogen with irregular contours (n) (%)	Total	X^2	*P* value
Patients with malignant LNs (n=161)	88 (30.2%)	71 (24.3%)	13 (4.4%)	119 (40.8%)	291 (100%)	35.08	$P<.001$
Patients with benign LNs (n=384)	365 (47%)	181 (23.3%)	43 (5.5%)	188 (24.2%)	777 (100%)		
Total number of patients (n=545)	453	252	56	300	1068		

LNs = Lymph nodes.
* The group where the difference originated

When malignant, anthracotic and reactive LNs were compared as to the internal structures, malignant LNs were most frequently seen in heterogeneous density (65.3%) group. While the rate of heterogeneous density was 57.5% in antharcotic LNs, the rate was seen as 45% in reactive LNs. The rate of homogeneous density was found to be significantly higher in reactive LNs (Table 9).

When malignant, anthracotic, reactive and other benign LNs were compared concerning the contours and internal structures, malignant LNs were most frequently found in heterogeneous density group with irregular contours (40.8%). Anthracotic LNs (38%), reactive LNs (47.4%) and other benign LNs (62.5%) were most frequently observed in homogeneous density group with regular contours. The images were statistically higher in homogeneous density group with regular contours in other benign LNs and heterogeneous density group with irregular contours in malignant LNs (Table 10).

Despite a rarely encountered entity throughout the world, the features of anthrcotic LNs, commonly seen in Turkey, are totally presented in Table 11.

Table 8

Rates of malignant, anthracotic and reactive lymph nodes according to the nature of contours.

	LNs with regular contours (n) (%)	LNs with irregular contours (n) (%)	Total	X^2	*P* value
Patients with malignant LNs (n=161)	159 (54.6%)	132 (45.4%)	291 (100%)	12.35	$P=.002$
Patients with anthracotic LNs (n=191)	271 (64.8%)	147 (35.2%)	418 (100%)		
Patients with reactive LNs (n=73)	84* (71.1%)	34 (28.8%)	118 (100%)		
Total number of patients (n=425)	514	313	827		

LNs = Lymph nodes.
* The group where the difference originated.

Table 9

Rates of malignant, anthracotic and reactive lymph nodes according to the internal structure.

	Homogeneous density (n) (%)	Heterogeneous density (n) (%)	Total	X^2	*P* value
Patients with malignant LNs (n=161)	101 (34.7%)	190 (65.3%)	291 (100%)	14.68	$P=.001$
Patients with anthracotic LNs (n=191)	178 (42.5%)	240 (57.5%)	418 (100%)		
Patients with reactive LNs (n=73)	65* (55%)	53 (45%)	118 (100%)		
Total number of patients (n=425)	344	483	827		

LNs = lymph nodes.
* The group where the difference originated

Table 10

Rates of malignant, anthracotic, reactive and other benign lymph nodes according to the nature of contours and internal structure.

	Homogen with regular contours (n) (%)	Heterogen with regular contours (n) (%)	Homogen with irregular contours (n) (%)	Heterogen with irregular contours (n) (%)	Total	X^2	*P* value
Patients with malignant LNs (n=161)	88 (30.2%)	71 (24.3%)	13 (4.4%)	119* (40.8%)	291 (100%)	78.61	*P*=.001
Patients with anthracotic LNs (n=191)	159 (38%)	112 (26.7%)	19 (4.5%)	128 (30.6%)	418 (100%)		
Patients with reactive LNs (n=73)	56 (47.4%)	28 (23.7%)	9 (7.6%)	25 (21.1%)	118 (100%)		
Patients with other benign LNs (n=73)	150* (62.5%)	41 (17%)	15 (6%)	35 (14.5%)	241 (100%)		
Total number of patients (n=545)	453	252	56	300	1068		

* The group where the difference originated. LNs = Lymph nodes.

4. Discussion

Mediastinal and hilar LAPs can result from malignant or many different benign diseases, are imaged with thorax CT and 18F-FDG PET/CT, and diagnosed with EBUS-TBNA in general. Since distinguishing between the malignant-benign cases and the differential diagnosis of these LAPs are of a vital importance, the procedures that will increase the diagnostic value of the procedures are still needed. In the study where 1075 patients were analyzed through EBUS-TBNA by Dabrowska et al., while the most frequent cause of mediastinal LNs was reported as malignant diseases (61.6%), lung cancers and other malignancies were detected as 53 and 8.4%, respectively. Among the benign diseases, the most common was sarcoidosis (23.3%).[18] In our study, anthracotic LNs were found as the most frequent malady (35%). Among the total malignancies (29.5%), the number of lung cancers and extrapulmonary malignancies was found to be 24.5% and 4.9%, respectively. In addition, sarcoidosis was diagnosed in 109 (20%) and reactive LNs in 73 (13.4%) patients (Table 2). It was considered that the reasons why the number of anthracotic LNs is so increased may be due to the higher rate of cigarette smoking (42.1% in men, 16.8% in women and 29.1% in total)[19] and exposure to biomass smoke in Turkey.

Table 11

In characteristics of anthracotic LNs.

In characteristics of anthracotic LNs	Patients (n)	Percent (%)
Patients with anthracotic LNs (Pathology of Final Diagnosis)	191	35
Total Anthracotic LNs	418	39
Anthracotic LNs with regular contours (n) (%)	271	64.8
Anthracotic LNs with irregular contours (n) (%)	147	35.2
Anthracotic LNs with homogeneous density (n) (%)	178	42.5
Anthracotic LNs with heterogeneous density (n) (%)	240	57.5
Anthracotic LNs with with homogen and regular contours (n) (%)	159	38
Anthracotic LNs with heterogen and regular contours (n) (%)	112	26.7
Anthracotic LNs with homogen and irregular contours (n) (%)	19	4.5
Anthracotic LNs with heterogen and irregular contours (n) (%)	128	30.6
Anthracotic LNs SUVmax value of 18F-FDG PET/CT (SUVmax, mean ± SD)	6.31 ± 4.3	

LNs = lymph nodes, 18FDG-PET/CT = fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography, SD = standard deviation, SUVmax = maximum standardized uptake value.

Composed of wood, and animal and plant wastes, biomass is still used as the largest source of energy in rural areas in Turkey. The share of wood, one of the biomass energy sources, is 14% in the total energy production of Turkey.[20] In the first major epidemiological study performed in Turkey, the exposure to biomass was demonstrated to be the common cause of chronic obstructive pulmonary disease among female patients living in rural areas at a significantly higher rate of 54.5%.[21]

The treatment of non-small cell lung cancer (NSCLC) includes the curative surgical resection for early-stage disease and the chemo-radiotherapy for advanced-stage disease. An accurate preoperative staging of mediastinal LNs is not only necessary to determine the appropriate treatment, but to avoid unnecessary invasive procedures including thoracotomy, as well. The sampling of mediastinal LNs can be performed using a variety of techniques, including mediastinoscopy, surgery (open or video-assisted thoracoscopic surgery), EBUS-TBNA or endoscopic USG-guided FNAB (EUS-FNAB).[22] Mediastinoscopy has been accepted as the standard reference for the mediastinal LNs staging of NSCLC.[23] However, while the samples can be obtained through the mediastinoscopy from the left upper paratracheal (2L), right upper paratracheal (2R), left lower paratracheal (4L) and right lower paratracheal (4R) stations, LNs cannot be sampled from of 10L, 10R, 11R, 8th and 9th stations.[24] In addition, mediastinoscopy also requires general anesthesia and is an invasive procedure. A recent meta-analysis of the studies comparing EBUS/EUS procedures with overall mediastinoscopy suggests the equivalence of the two procedures.[24] The current practice is to perform mediastinoscopy with the aim of staging to rule out false negativity in those with EBUS-TBNA/EUS-FNAB negativity.[25] There are many studies revealing the diagnostic value of EBUS-TBNA. In a recently published study in which the findings of 10-year follow-up were assessed, Carrasco et al. reported that mediastinal malignancies were found in 14 of 81 negative cases consisting of a series of 616 EBUS-TBNA procedures and NPV of EBUS was found as 83%.[26] In the differentiation between benign and malignant LNs in our study, the sensitivity specificity, PPV and NPV of EBUS-TBNA were calculated to be 79.5, 98.1, 89.5 and 91.7%, respectively.

In a study where the findings of EBUS-TBNA were evaluated in terms of mediastinal or hilar LNs in extrapulmonary malignancies in the Turkish population, malignant and benign results were obtained in 18 patients (28.5%) and 45 patients (71.5%) respectively out of 63 cases where 138 LNs were sampled with EBUS-TBNA. In the benign group, false negative LNs in five (7.9%), anthracotic LNs in 13 (20.6%), reactive LNs in 16 (25.3%), sarcoidosis in seven (11.1%) and tuberculosis in 2

(3.1%) were detected. The sensitivity, specificity, PPV, and NPV of EBUS-TBNA were reported as 78.2, 100, 100, and 88.3%, respectively.[11] The diagnostic values and the rate of anthracotic LNs in this study were similar to our findings. In our study, the percentages of diagnosis were found as 35% for anthracotic LNs, 24.5% for lung cancers, 4.9% for extrapulmonary malignancies, 20% for sarcoidosis, 13.4% for reactive LNs and 1.2% for TB lymphadenitis (Table 2).

In several studies performed nearly 10 years ago, it was reported that 18F-FDG PET/CT made biological assessment possible and was considered a reliable method for staging lung cancers and had high sensitivity (81%–92%) and specificity (73%–85%) rates.[27,28] Even so, it has been reported in recent studies that the sensitivity was high while the specificity rate was found to be low.

In a study performed by Yu et al, the diagnostic sensitivity, specificity, PPV and NPV of 18F-FDG PET/CT were detected as 89.2, 32.3, 61.7, and 71%, respectively.[29] Likewise, in another study by Erer et al., the diagnostic sensitivity, specificity, PPV and NPV of 18F-FDG PET/CT were reported to be 85, 29.4, 42.8, and 83.3%, respectively.[11] In another study where 322 patients were investigated in terms of the correlation between malignancy probability and mediastinal LNs SUVmax values sampled through EBUS-TBNA in 18F-FDG PET/CT scanning, it was demonstrated that as SUVmax increased, malignancies were likely to increase. However, given the cut off value as nine for SUVmax, while the specificity was seen high (79.1%), the sensitivity rate was found low (54.39%).[1] There are a limited number of comprehensive studies evaluating the cytological, radiological and clinical features of LNs found positive in 18F-FDG PET/CT. In the study in which the experiences of a large cancer center obtained from 577 LNs were evaluated, 263 (46%) patients were compared with those having PET-CT positivity and malignant cytology, and 314 (54%) patients were compared with those having PET-CT positivity and cytology-benign LNs groups. Average SUVmax value was found to be significantly higher in those with PET-CT positivity and malignant cytology (10.05 and 5.99).[30] In our study, of 545 patients 1068 LNs were sampled from, 270 underwent 18F-FDG PET/CT scanning. The mean SUVmax value (11.02) of the malignant LNs obtained from 132 patients was found to be significantly higher, compared with the mean SUVmax value (6.48) of the benign LNs of 138 patients ($P < .05$) (Table 3). In the differentiation between malignant and benign LNs, considering the values of 18F-FDG PET/CT SUVmax as 2.72 according to ROC curve, the sensitivity and specificity rates were found as 99.3 and 11.7%, respectively. However, given that the cut off value was taken 6.48 as the mean SUVmax of benign LNs, the sensitivity, specificity, PPV and NPV were calculated as 76.5, 64, 20.49, and 78.38%, respectively.

In light of these findings, it can be suggested that PET-CT positivity is not specific for malignancy and may be insufficient to guide the management of the patients with mediastinal LAPs. For this reason, researchers have been maintaining various studies in order to increase the diagnostic value of PET-CT. In a study where the diagnostic values of the size and images of LNs were examined through thorax CT and 18FDG PET/CT, it was reported that when the size of LNs and SUVmax values were combined, the specificity rate could be increased in diagnosis.[30]

In a similar study investigating LN metastases in NSCLC, the sensitivity of thorax CT and PET/CT was reported to be lower in normal-sized (short axis < 10 mm) LNs in. In this study, EBUS or endo-esophageal USG (EUS) was performed in 161 cases with NSCLC where no metastasis of LNs was detected through these two methods, and a total of 416 LNs biopsies were performed in 161 patients. Of 161 patients, 21 (13%) showed the positivity of malignancy in endosonographic staging. Therefore, in the presence of radiologically normal mediastinal LNs, the staging of combined endosonographic LNs has been proposed in the pre-treatment staging of high-risk patients with NSCLC.[31] This study suggests that ultrasonographic data be used more widely in the diagnosis of mediastinal and hilar LNs.

In a recent review performed in Japan, it has been stated that EBUS-TBNA is a low-invasive method with excellent sensitivity, specificity and accuracy in the diagnosis of LNs metastasis of lung cancer, and so is the first choice as an alternative to mediastinoscopy, which has long been the gold standard for the nodal staging of NSCLC. It was also reported that USG technology used in EBUS provides adequately the sampling of especially suspected lesions, and that the efforts to develop USG imaging technology are still maintained.[32]

There are limited number of studies on the diagnostic value of USG images of mediastinal and hilar LNs. In the study where a total of 1.061 LNs from 487 patients were retrospectively investigated by Fujiwara et al, the sonographic features of LNs based on the classification of EBUS imaging were reported to be beneficial in the prediction of metastatic LNs during EBUS-TBNA. In this study, such features as round shape, prominent contour structure, heterogeneous echogenicity and the presence of coagulation necrosis sign were found to be significantly higher in malignant LNs than benign LNs.[33]

Similarly, in another recently published study on the same subject, while the findings, such as round shape, heterogeneous echogenicity, hyperechogenicity, prominent contours and necrosis were found to be significantly higher in malignant LNs, the presence of calcification and central hilus structure were significantly higher in benign LNs.[34] In our study, the features of the contours and internal structure in LNs were investigated both in the differentation between malignant and benign results, and among the subgroups of benign LNs, including reactive, anthracotic and other benign LNs.

In our study, 54.6% of 291 LNs obtained from 161 patients with malignancy were with regular contours, as consistent with the findings of other studies. However, unlike other studies, most of the benign LNs in our study had regular contours; in other words, 70.2% of 777 benign LNs obtained from 384 patients were with regular contours, while 29.8% had irregular contours (Table 5). Compared LNs in terms of the features of internal structure, 65.3% of malignant LNs were seen to be in heterogeneous density group (Table 6).

Unlike other studies, considering both the contours and features of internal structure, it was found that while the heterogeneous structure with irregular contours was seen to be significantly higher in malignant LNs, the homogeneous structure with regular contours was found significantly higher in benign LNs (Table 7).

In anthracosis, not only are the lung parenchyma and bronchioles influenced, but the lymphatic system is also affected, resulting in chronic LAPs and nodal enlargement.[8] In a study investigating thorax CT findings of anthracotic LNs, the contour nature of 66% of anthracotic LNs was reported to have regular contours.[8] Performed in Turkey, another study reported the sonographic features of anthracotic LNs that the structure of contours was prominent (73.6%), the internal structure was heterogeneous (50.7%) and the shape was oval as (52.7%).[9] In

our study, when the anthracotic and reactive LNs were assessed in terms of the structure of contours, both groups of LNs were found to have prominently regular contours (64.8% and 71.1%, respectively) (Table 8). While the internal structure of anthracotic LNs was found to be mostly heterogeneous (57.5%), the internal structure of reactive LNs was mostly homogeneous (55%) (Table 9).

When the malignant, anthracotic, reactive and other benign LNs were compared as to both the features of contours and internal structure, we found that malignant LNs were most frequently seen in heterogeneous density group with irregular contours, while others were most frequently in homogeneous density group with regular contours. The statistically significant difference between LNs arose from the malignant and other benign LNs groups (Table 10).

5. Limitations

Since our study was designed as a retrospective study, the investigations of 18F-FDG PET/CT were found merely in 270 of 545 patients within the period one month before and after EBUS-TBNA was performed in our scanning. So, 18F-FDG PET/CT examinations were not available for all participants. Real-time USG images of mediastinal and hilar LNs during EBUS-TBNA were described and classified by the chest diseases specialists. We do not know whether our study findings would have been affected, if the images had been evaluated by a radiologist. Another limitation was that we had no opportunity to assess the cytological results rapidly in situ during EBUS-TBNA.

6. Conclusion

The diagnostic value of 18FDG PET/CT is not sufficient for the diagnosis of mediastinal and hilar LAPs. As a radiation-free, cheap and easily accessible modality, endobronchial USG images can contribute to the differential diagnosis of malignant, anthracotic and other benign LNs, and such contributions can guide clinician bronchoscopists during EBUS-TBNA. Meanwhile, the morphological features of LNs obtained based on the images of EBUS may play a role in predicting malignancies. The biopsies to be performed in light of this information may increase the diagnostic value of EBUS-TBNA. It may be postulated that the triple modality may provide correct staging and increase survival rate in those with lung cancer by contributing to the determination of maximum therapeutic strategy. However, sampling a lymph node solely based on the morphology cannot be ruled out safely.

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