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ORIGINAL ARTICLE – OPEN ACCESS

An Assessment of the Adequacy of Endobronchial Ultrasound to Assess Mediastinal Lymph Nodes Accompanying Extrathoracic Malignancies

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ABSTRACT

Objective: Correct sampling with a targeted diagnosis of pathological mediastinal lymph nodes (LNs) accompanying extrathoracic malignancies (ETMs) is necessary to grade tumors and evaluate the treatment response. However, debate continues about the adequacy of endobronchial ultrasound (EBUS) assessment. This study was designed to determine the efficiency and reliability of EBUS in the diagnosis of mediastinal LNs in patients with ETMs.

Materials and Methods: A retrospective analysis was conducted of patients with suspicious mediastinal LNs accompanying ETM observed at diagnosis or in follow-up who underwent EBUS. The data assessed were age, gender, ETM, LN diameter observed in both computed tomography (CT) and EBUS, LN metabolic activity recorded with positron emission tomography (PET)-CT, the histopathological diagnosis of LNs sampled using EBUS, and the actual LN diagnosis based on mediastinoscopic LN sampling or radiological stability.

Results: Samples were taken from a total of 78 LN stations from 50 patients with a mean age of 61.28±10.92 years. Of 22 LNs with actual malignancy, 16 were identified with EBUS. The mean LN diameter determined with CT and EBUS, and the mean PET-CT maximum standard uptake (SUV_{max}) value was 17.36±7.90 mm, 22.90±9.87 mm, and 8.17±5.44, respectively. The malignant LN diameter measured using both CT and EBUS was significantly higher than that of benign LNs (respectively p=0.001, p=0.026). There was no significant difference between the SUV_{max} values of malignant and benign LNs.

Conclusion: As some of the LNs found to be reactive with EBUS were malignant, we recommend confirming the diagnosis with mediastinoscopy sampling or radiological follow-up.

Keywords: Breast cancer, cancer, endobronchial ultrasound, extrathoracic malignancies, mediastinal lymph nodes

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INTRODUCTION

Endobronchial ultrasound (EBUS) is a minimally invasive diagnostic method that has proven efficacy and reliability for the diagnosis of pathological mediastinal and hilar lymph nodes (LNs) (1). Due to the high sensitivity and specificity as well as lower morbidity and mortality rates it offers and no requirement for hospitalization, it is now often preferred to mediastinoscopy to grade primary lung cancer. However, the precise role of EBUS in the diagnosis of pathological mediastinal and hilar LNs accompanying extrathoracic malignancies (ETMs) has not yet been clarified. There are few studies on this subject, and these have examined only a small number of cases (2, 3).

In cases of ETM, a pathological mediastinal or intrathoracic LN identified at the time of diagnosis or during follow-up raises concerns of severe malignancy because metastasis to the mediastinum has been seen to develop in 30% of EMT (4, 5). An enlarged LN determined using computed tomography (CT) or a hypermetabolic LN determined using positron emission tomography (PET)-CT could be malignant. Previous studies have reported that mediastinal and hilar LNs showing high metabolic activity were associated with sarcoidosis and tuberculosis in patients with ETM (6). Importantly, there can be significant confusion between a primary tumor and mediastinal and hilar LNs with increased activity or which emerge as a response to malignancy treatment. ETM management can be difficult without a differentiation between sarcoid-like reaction, tuberculosis, or metastasis. The benefits of PET-CT in this differentiation in patients with ETM are limited.

The aim of this study was to retrospectively examine the primary malignancies and radiological findings of patients with ETM who underwent EBUS and several characteristics of the EBUS diagnoses, and to present the analysis results in the context of the literature.

MATERIALS and METHODS

Ethics Committee Approval

Approval for this study was granted by the Ethics Committee of Antalya Training and Research Hospital on July 27, 2020 (no: 13/13).

Study Design and Participants

The records of patients with known ETM and suspicious mediastinal/hilar LNs determined on CT or PET-CT images at the time of diagnosis or during follow-up and who underwent EBUS in the Chest Diseases Clinic of Antalya Training and Research Hospital between March 1, 2018 and December 1, 2019 were retrospectively analyzed. All of the patients who underwent EBUS examination had a mediastinal/hilar LN evaluation with PET-CT, and patients with short axis ≥10 mm and maximum standardized uptake (SUV_{max}) value ≥2.5 LN measurements underwent EBUS.

EBUS Procedure

The EBUS procedure was performed in the operating theater under conscious sedation with midazolam and propofol using a Fujinon EBUS device (7.5 mhz EB-530US/Sonart SU-1; Fujinon/Fujifilm Corp., Tokyo, Japan). During the procedure, mediastinal and hilar LNs (2R, 4R, 10R, 11R, 7, 11L, 10L, 4L, 2L, etc.) were systematically evaluated with EBUS, and at least 3 samples were taken from LN stations with involvement as determined by PET-CT.

Final Diagnosis

The diagnosis of a benign LN obtained with EBUS was confirmed surgically or with 1 year of radiological follow-up. A total of 3 patients with incomplete data and from whom LN samples could not be obtained in the EBUS procedure were excluded from the study. In all, the data of 50 patients were analyzed.

Statistical Analysis

In this study, the general characteristics, disease state, and scores of the patients were described using mean, deviation, percentage, and frequency. The Mann-Whitney U test was used for proportional-type variables to examine the general characteristics and disease state of the patients of groups categorized as malignant and benign. The Mann-Whitney U test was also used to compare SUV measurements in the 2 groups. The Kruskal-Wallis test was applied to examine whether the LN SUV measurements of the benign group differed, and all pairwise comparisons were used to evaluate pairs. IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA) was used to perform the analysis and α=0.05 was considered significant.

RESULTS

General Characteristics of the Patients

Samples were taken from a total of 78 LN stations from 50 patients. The study group comprised 26 (52%) females and 24 (48%) males with a mean age of 61.28±10.92 years. The mean LN diameter determined with CT was 17.36±7.90 mm. The mean LN SUV_{max} measurement determined with PET-CT was 8.17±5.44. The mean short axis of LNs measured with EBUS was 22.90±9.87 mm (Table 1).

EBUS examination resulted in a diagnosis of a malignant LN in 16 patients and a benign LN in 34 patients. Ultimately, it was determined that the nodes were malignant in 22 patients and benign in 28; the EBUS results led to a misdiagnosis of a benign characterization in 6 patients.

Table 1. General characteristics of the patients

Patient characteristics	
Gender, n (%)	
Female	26 (52)
Male	24 (48)
Measurements (Mean±SD)	
Age (years)	61.28±10.92
CT or PET-CT lymph node diameter (mm)	17.36±7.90
PET-CT lymph node SUV_{max}	8.17±5.44
EBUS size (mm)	22.90±9.87

CT: Computed tomography; EBUS: Endobronchial ultrasonography; PET-CT: Positron emission tomography; SUV_{max}: Maximum standard uptake value; SD: Standard deviation

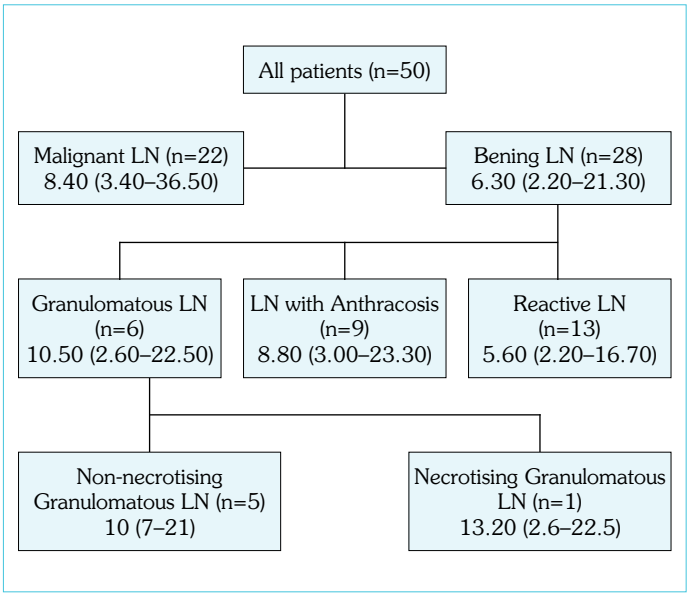

Figure 1. The mean lymph node SUV_{max} values according to the diagnosis group (n, mean±SD)

A significant difference was determined between the LN diameter determined with CT or PET-CT of the patients with a final diagnosis of benign or malignant LN, and the mean node diameter of the malignant LNs was significantly greater (p=0.001) (Table 2). The mean LN diameter measured with EBUS was greater in the malignant group (p=0.026).

No significant difference was determined between the malignant and benign LNs in terms of the SUV_{max} value (p=0.110). In the benign subgroups, the SUV_{max} value of both necrotizing and non-necrotizing granulomatous lymphadenitis was significantly higher than that of the other benign subgroups (reactive and anthracosis) (p=0.01, p=0.01, respectively). In the comparison of benign and malignant LNs, the SUV_{max} value in both necrotizing and non-necrotizing granulomatous lymphadenitis was found to be significantly higher than that of malignant LNs (p=0.03, p=0.03, respectively) (Fig. 1).

Table 2. Lymph node measurement values and stations according to the final diagnosis groups

Measurement	Group		p
	Benign (n=28) μ (Min–Max)	Malignant (n=22) μ (Min–Max)	
CT or PET-CT lymph node diameter (mm)	13 (10–29)	18 (10–40)	**0.001***
Lymph node SUV_{max}	6.30 (2.2–21.3)	8.40 (3.4–36.5)	0.110
EBUS size (mm)	14.25 (9.4–35.43)	35.43 (10.4–40)	**0.026***
Age (years)	61 (41–77)	61 (80–37)	0.981
Lymph node station			
2R	1 (2.4%)	3 (8.1%)	
3P	0 (0%)	2 (5.4%)	
4R	8 (19.5%)	8 (21.6%)	
4L	0 (0%)	3 (8.1%)	
7	20 (48.8%)	10 (27%)	
10R	0 (0%)	5 (13.5%)	
11R	4 (9.8%)	4 (10.8%)	
11L	8 (19.5%)	2 (5.4%)	
Total	41	37	

*: 0.05 level of statistically significant difference; CT: Computed tomography; EBUS: Endobronchial ultrasonography; PET-CT: Positron emission tomography; SUV_{max}: Maximum standard uptake value; Min: Minimum; Max: Maximum

Table 3. Distribution of the final lymph node diagnoses

Benign (n=28)			Malignant (n=22)		
Diagnosis	**n**	**%**	**Diagnosis**	**n**	**%**
Reactive	13	46.4	Breast Ca	7	31.8
Anthracosis	9	32.1	Cervical Ca	4	18.2
Non-necrotizing GL	5	17.9	Esophagus Ca	3	13.6
Necrotizing GL	1	3.6	Colon Ca	2	9.1
			Prostate Ca	2	9.1
			Renal cell Ca	2	9.1
			Larynx Ca	1	4.5
			Bladder Ca	1	4.5

Ca: Cancer; GL: Granulomatous lymphadenitis

The results of this study showed that ETMs can metastasize to many different mediastinal and hilar LNs. The 2L station was not sampled in this study, as it was indicated by CT or PET-CT findings. The diagnosis of malignant or benign varied in other LNs: All of the samples obtained from 3P, 4L, and 10R were diagnosed as malignant. The nodes sampled and the distribution of benign and malignant diagnoses are shown in Table 2.

It was observed that many different ETMs metastasized to mediastinal or hilar LNs. The most common was breast cancer (31.8%). The most frequent benign diagnosis was a reactive node. A diagnosis of granulomatous lymphadenitis was made in a total of 6 patients: 5 non-necrotizing and 1 necrotizing. The distribution of the LN diagnoses is shown in Table 3.

DISCUSSION

Accurate sampling with a targeted diagnosis of pathological mediastinal LNs accompanying ETMs is necessary for grading and for evaluating response to treatment. However, debate continues about the adequacy of EBUS to evaluate mediastinal LNs in cases of ETM. This retrospective examination included the results of 50 patients with ETM who underwent EBUS examination. Of 22 nodes with actual malignancy, 16 were correctly identified with EBUS; 6 malignant nodes were diagnosed as benign. The study results demonstrated that the primary types of cancer metastasizing to mediastinal and hilar LNs were breast, cervical, esophagus, colon, kidney, prostate, larynx, and bladder cancer. The extrathoracic cancer type creating the most metastasis was breast cancer. The diameter of the malignant LNs measured both with tomography and with EBUS was significantly greater than that of benign nodes. PET-CT results indicated that the benign LNs were as hypermetabolic as the malignant nodes. No significant difference was seen between the total SUV_{max} values of benign and malignant nodes. However, the SUV_{max} values of the benign subgroup of granulomatous lymphadenitis were higher than those of malignant nodes. Granulomatous nodes in the benign group explain the lack of significant difference between the SUV_{max} values. The SUV_{max} values of the reactive and anthracotic LNs were significantly lower than those of the malignant nodes.

EBUS provides an opportunity for simultaneous imaging and sampling of mediastinal and hilar LNs. It is also less invasive than mediastinoscopy (1). Several studies have recently examined the role of EBUS in the diagnosis of mediastinal or hilar LNs accompanying ETM (7–9). In a series of 92 patients who underwent EBUS due to a suspicion of mediastinal or hilar LN metastasis,

the authors determined an EBUS sensitivity of 85% and negative predictive value of 76% for malignancy (8). Song et al. (2) reported the results of 57 patients with suspected ETM who were evaluated with EBUS and found that the diagnostic sensitivity of EBUS was 88%, accuracy was 93%, and the negative predictive value was 85%. In 39 patients with ETM, Park et al. (9) reported an EBUS sensitivity of 96.35% and a specificity of 100%. Furthermore, in a real-life study, it was observed that EBUS confirmed malignancy and avoided a surgical procedure for 50.3% of patients with metastatic mediastinal LN accompanying ETM (10). In a recently reported article about EBUS in ETM cases with suspected mediastinal LN metastasis, it was noted that the specificity, positive predictive value, negative predictive value, and diagnostic accuracy of EBUS-transbronchial needle aspiration was 76.19% (95% confidence interval [CI]: 52.83–91.78), 100% (95% CI: 95.89–100.00), 100% (95% CI: 89.12–97.12) and 95.4%, respectively (11). In the current study, EBUS provided a highly accurate malignant and benign differentiation. All of the patients diagnosed with benign LNs with EBUS were evaluated again with radiological follow-up or mediastinoscopy, and a misdiagnosis had been made in only 6 patients, which were found to be the result of a reactive node rather than metastasis. These findings support earlier results indicating that EBUS provides an opportunity to diagnose the majority of pathological mediastinal and hilar LNs accompanying ETM without the need for mediastinoscopy.

The determination of mediastinal LN metastasis is important in the management of ETM. The first test usually requested for grading or evaluating response to treatment is CT or PET-CT. Concerns of malignancy increase with the size of the node. It has been previously reported that increased LN size in non-small-cell lung cancer is associated with an increased risk of malignancy (7). A significant relationship has been demonstrated between malignancy and node size in ETM (7, 12). The current study illustrated a significant relationship between malignancy and node size measured with both EBUS and tomography. The size of malignant LNs was significantly greater than that of benign nodes. However, even a normal size may not always mean that the node is benign. PET-CT has been reported to be better than CT for the determination of metastatic LNs (13). While hypermetabolic mediastinal LNs visualized with PET-CT may be metastatic, they may also be associated with active tuberculosis, sarcoidosis, and inactive diseases, such as previous tuberculosis, silicosis, and anthracosis (6, 14). In particular, the high fluorodeoxyglucose (FDG) involvement seen in sarcoidosis and tuberculosis can suggest severe malignancy. In countries where tuberculosis is endemic, tuberculous lymphadenitis accompanying ETM may be more common than thought and PET-CT results of a hypermetabolic mediastinal LN may mimic metastasis. Sarcoidosis develops in approximately 3% to 17% of all cancer patients (15, 16).

A sarcoid-like reaction may accompany many different malignancies, such as hematological malignancies, cancer of the testis or breast, gastrointestinal system tumors, and gynecological tumors (15–18). It is thought that sarcoid-like reactions occur as a result of the host immune response to dispersed tumor cells (19). The increased use of PET in cancer patients for grading or evaluation of response to treatment has revealed more sarcoid-like reactions and tuberculous lymphadenitis (20–23). Zheng et al. (24) reported that in 25 patients diagnosed with lung tuberculoma, FDG involvement was negative in the PET-CT scan of only 1 patient. In addition, hypermetabolic activity has been seen in cases of sarcoidosis or anthracosis on PET-CT (25–27). In the current study, it was observed that LNs could be hypermetabolic in cases of reactive lymphadenitis, anthracosis, and granulomatous diseases, and that metabolic activity was not a marker for malignant-benign differentiation. The metabolic activity in granulomatous lymphadenitis associated with sarcoidosis and tuberculosis was significantly higher than that of metastatic LNs.

There are some limitations to this study, primarily the retrospective design and a relatively small number of patients. These limitations could be overcome with a prospective study that enrolls a larger number of patients with well-defined inclusion and exclusion criteria. Some of the benign LNs were confirmed with mediastinoscopy. The regression or stability of findings in 1-year radiological follow up of the remainder was accepted as supporting the benign diagnosis made based on EBUS results.

In conclusion, while mediastinal and hilar lymphadenopathy in ETMs may be metastatic, it may also originate from benign diseases, such as tuberculosis, sarcoidosis, and anthracosis. In the current study, the LN diameter measured with tomography or EBUS was significantly greater in cases of malignancy. Reactive and anthracotic LNs may be hypermetabolic on PET-CT, but FDG involvement is significantly lower when compared with metastatic nodes, whereas the metabolic activity of granulomatous lymphadenitis, such as tuberculosis and sarcoidosis, was greater than that of malignancies. PET-CT is not sufficient for the differentiation of malignant and benign LNs accompanying ETMs. In the current study, many metastatic LNs could be diagnosed with EBUS without the need for mediastinoscopy. However, some of the nodes determined to be benign (reactive) with EBUS were actually found to be malignant. Therefore, confirmation of the diagnosis of reactive LNs according to EBUS is recommended.

Ethics Committee Approval: The Antalya Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 27.07.2020, number: 13/13).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Conflict of Interest: The authors have no conflict of interest to declare.

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