Efficacy of Endobronchial Ultrasound-Guided Transbronchial Needle Biopsy for the Diagnosis of Intrathoracic Lymph Node Metastases from Extrathoracic Malignancies

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Abstract

Objective: Intrathoracic lymph node enlargement is common among patients with extrathoracic malignancies. While endobronchial ultrasound-guided-transbronchial needle aspiration (EBUS-TBNA) is often used for diagnosing mediastinal or hilar lymph nodes and for staging lung cancer, there are still a few studies demonstrating the use of EBUS-TBNA for determining intrathoracic metastases from extrathoracic malignancies. The aim of this study is to evaluate the role of EBUS-TBNA for the diagnosis of extrathoracic malignancies.

Methods: From March 2010 to July 2015, 190 patients with known extrathoracic malignancy, who underwent diagnostic convex probe (CP)-EBUS-TBNA due to suspicion of metastases, were included in the study. The patients' data were retrospectively investigated.

Results: The findings of EBUS-TBNA were examined; 61 patients (32%) were malignant, 121 (63%) were benign, and 3 (1.5%) were not diagnostic. Five patients (3.5%) were not sampled because of the millimetric size of the lymph nodes. There was no progression at the 12-month follow-up in these patients. Among the malignancy patients, 40 had extrathoracic malignancy-related intrathoracic metastases. The diagnosis of the lymph nodes with EBUS-TBNA and the final diagnosis at follow-up are given as summarized. The size of the lymph node decreased during clinical follow-up in one of the three non-diagnostic patients (accepted as having reactive lymph node). The other two patients were diagnosed as malignant using mediastinoscopy (having esophageal cancer and squamous cell lung cancer). The sensitivity was found to be 95.3%, specificity was 100%, the negative predictive value was 97.6%, and the diagnostic accuracy rate was 98.4%.

Conclusion: EBUS-TBNA is a simple, reliable, and adequate diagnostic method for determining intrathoracic lymph node metastases related to known extrathoracic malignancies.

Keywords: Biopsy, endobronchial ultrasonography, extrathoracic malignancy, metastases

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INTRODUCTION

The thorax is an area in which distant metastases are frequently observed because it is located on the hematologic and lymphatic pathways (1). Various malignant neoplasms can metastasize to the lung (parenchymal or endobronchial), the hilar-mediastinal lymph nodes, pleura, pericardium, or to the chest wall. The lungs and mediastinum, especially, are the places where other malignancies often metastasize. Most commonly, breast, colon, and renal cancers metastasize to the lung (2, 3). However, they may not all be mediastinal lymph node metastases; simultaneously, it should also be considered that it could be granulomatous disease or primary lung cancer. The early detection of mediastinal metastases is important for the treatment and prognosis of the primary malignancy (4).

Along with the imaging methods [computerized tomography (CT), positron emission tomography-CT (PET-CT), and magnetic resonance imaging (MRI)] for the diagnosis of intrathoracic lymph nodes, en-

dobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), mediastinoscopy (MS), and open lung surgery are also used. MRI, CT, and PET are effective in the detection of lymph nodes, but they are insufficient for clinical decision-making due to the lack of tissue diagnosis (5). Although MS and open lung surgery are standard methods for staging, they are more invasive, expensive, and also require general anesthesia (6-8). EUS-FNA is a minimally invasive method; however, it is insufficient to evaluate the right paratracheal and hilar lymph nodes (9, 10). EBUS-TBNA is also a minimally invasive method used for the diagnosis of mediastinal or hilar lymph nodes (11). Recently, there have been a few studies on the lymph node metastases of extrathoracic malignancies detected using EBUS-TBNA (1-2, 12). Nevertheless, the role of EBUS-TBNA in determining mediastinal-related extrathoracic malignancies or hilar lymph node metastasis has not been fully determined (13). The aim of this study is to evaluate the role of convex probe (CP)-EBUS-TBNA with a linear probe (straight-convex) in the diagnosis of extrathoracic malignancies that metastasize to the mediastinum.

METHODS

Patient Group

In our clinic, from March 2010 to July 2015, 190 patients with known extrathoracic malignancy, who underwent diagnostic CP-EBUS (7.5 MHz, BF-UC160F; Olympus Optical Co., Tokyo, Japan) TBNA due to suspicion of metastases, were included in the study. The patients' data were retrospectively investigated. The demographics of the patients, primary malignancies, EBUS findings, and the cytologic and pathologic findings were recorded. The ethics committee of our institution approved the study. Informed consent was obtained from each patient.

Procedure

All EBUS-TBNA processing was performed with the help of an anesthetist, using midazolam, propofol, or ketamine with conscious sedation. The patients who had pathological lymph nodes (short axis >10 mm) with or without lesions in the lung parenchyma in CT, and/or showed 2-fluoro-2-deoxy-D-glucose involvement (SUV >2.5) in PET-CT were included in the study (Figure 1). All patients were evaluated by fiber optic bronchoscopy (FOB) before EBUS-TBNA; endobronchial lesions or mucosal irregularity were not observed. Each lymph node station reached using CP-EBUS was evaluated. Each lymph node considered to be pathologic was sampled an average of three times (Figure 2). Samples were placed in a container beside alcohol and formaldehyde for the cell block and also dried in room air. A part of each sample was isolated for the identification of *Mycobacterium tuberculosis* [using direct examination, Lowenstein culture, and Xpert is must be replaced to genexpert test which detects the DNA in TB bacteria (molecular genetic test)].

The malignant or benign diagnosis of the samples was established by immunohistopathological examination (Figure 3a, b). Benign patients were followed up for an average of one year; malignancy, as determined clinically and radiologically, was not seen.

Two of the three patients who had no diagnosis with EBUS-TBNA were diagnosed with esophagus CA and lung CA using mediastinoscopy; the other patient was accepted as having a negative malignancy because the lymph node size decreased after the one-year follow-up.

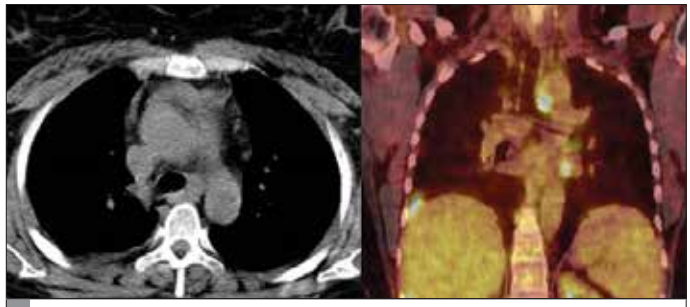

Figure 1. Thorax CT and PET-CT showing the left lower paratracheal lymph node (4L) of the patient, performed by EBUS-TBNA
PET-CT: positron emission tomography-computerized tomography; EBUS-TBNA: endobronchial ultrasound-guided-transbronchial needle aspiration

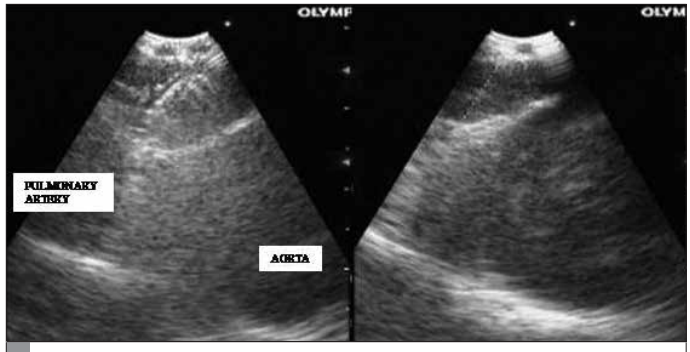

Figure 2. The view of the left lower paratracheal lymph node (4L) with EBUS showed hyperechogenicity, a pathological renal cell carcinoma
EBUS: endobronchial ultrasound

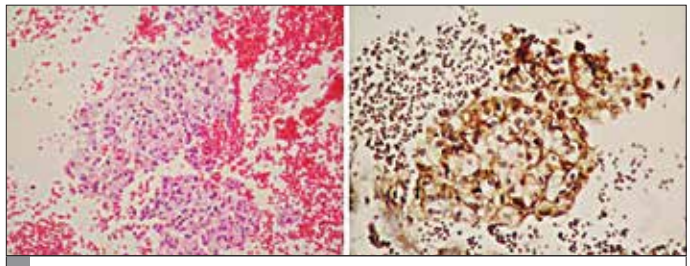

Figure 3. Renal cell carcinoma in cell block (HEX200) and RCC positivity in tumor cells (RCCX400)
RCC: renal cell carcinoma

Statistical Analysis

Sensitivity, specificity, negative predictive value, and diagnostic accuracy were evaluated using standard formulas. Statistical analyses were performed using the program Statistical Package for the Social Sciences (SPSS 20.0 version IBM Corp.; Armonk, NY, USA).

RESULTS

One hundred ninety patients admitted with the diagnosis of known extrathoracic malignancy were included in the study. Among the patients, 105 were male and 85 were female. The detailed demographics of the patients are shown in Table 1. While investigating the thorax CTs of the patients included in the study, the patients with only lymph node involvement were found to be the majority. However, 24% of the patients had a single solid nodule/mass in the lung parenchyma along with lymph node involvement (Table 2).

Table 1. Demographics (N=190)

Gender	105 M, 85 F		
Age	53 (±4.2)		
Extrathoracic malignancies (N (%))			
Breast carcinoma	43 (22.5)	Testicular carcinoma	4 (2.4)
Larynx carcinoma	22 (11.5)	Ovarian carcinoma	4 (2.4)
Gastric carcinoma	14 (7.5)	Unknown primary squamous cell carcinoma	3 (1.6)
Bladder carcinoma	11 (5.5)	Endometrial carcinoma	3 (1.6)
Colon carcinoma	10 (5)	Malignant melanoma	3 (1.6)
Renal cell carcinoma	9 (4.5)	Esophagus carcinoma	2 (1)
Thyroid carcinoma	8 (4.4)	Nasopharynx carcinoma	2 (1)
Prostate carcinoma	8 (4.4)	Cholangiocellular carcinoma	2 (1)
Cervical carcinoma	7 (3.8)	Tongue carcinoma	2 (1)
Rectal carcinoma	5 (2.6)	GI** Lymphoma	2 (1)
Mouth base mesenchyma, palate, and labium carcinoma	5 (2.6)	Glial TM**	2 (1)
Multiple carcinomas	5 (2.6)	Others*	14 (7.5)

*Other carcinomas (Parotid, ampulla of Vater, hepatocellular, maxillary sinus, soft tissue sarcoma, hypopharynx, nasopharynx, thymoma, pancreas, anal carcinoma, external ear canal, Ewing's sarcoma, nose, and Castleman disease); GI: gastrointestinal; TM: tumor

Table 2. Thorax computed tomography findings

Results	N (%)
Only lymph node	126 (66.3)
Lymph node+solid nodules/mass	45 (23.7)
Lymph node+multiple nodules/mass	19 (10)

Table 3. Distribution of sampled lymph node stations

Lymph node stations	Number of patients (n)
2R	6
2L	2
3P	1
4R	75
4L	30
7	117
10R	11
10L	5
11R	36
11L	50

Table 4. Distribution of intrathoracic metastatic malignancies diagnosed by EBUS-TBNA

Malignancies	Number of patients	Malignancies	Number of patients
Breast carcinoma	17	Cholangiocellular carcinoma	1
Renal Cell carcinoma	6	Hepatocellular carcinoma	1
Nasopharynx carcinoma	2	Ampulla of vater tumor	1
Thyroid carcinoma	2	Bladder carcinoma	1
Cervical carcinoma	2	Testicular carcinoma	1
Ovarian carcinoma	1	Prostate carcinoma	1
Gastric carcinoma	1	Rectal carcinoma	1
Colon carcinoma	1	Thymoma	1

EBUS-TBNA: endobronchial ultrasound-guided-transbronchial needle aspiration

In total, 333 lymph nodes were sampled by aspirating each lymph node three times in 190 patients. The distribution of the lymph nodes according to the stations is shown in Table 3.

The findings of EBUS-TBNA were examined; 61 patients (32%) were malignant, 121 (63%) were benign, and 3 (1.5%) were not diagnostic. Although high SUV uptake in lymph nodes were seen in PET-CT, the lymph nodes could not be sampled because they were millimetric in five patients. Progression was not detected in five patients from whom samples were not taken during the 12-month follow-up. Among the malignancy patients, 40 had extrathoracic malignancy-related intrathoracic metastases, 18 had lung CA, one had Hodgkin's lymphoma, and two had other malignancies. These two patients, whose cell type could not be determined with EBUS-TBNA, were diagnosed via mediastinoscopy as having squamous cell lung CA. The distribution of the extrathoracic malignancies (in 40 patients) with intrathoracic metastases, diagnosed by EBUS-TBNA, is shown in Table 4.

Six of the 121 benign patients were accepted as having reactive lymph nodes because lymph node size decreased during the 12-month follow-up. Anthracosis was detected with EBUS-TBNA in 87 patients, sarcoidosis was determined in 25 patients, and tuberculosis was determined in 3 patients. Patients with anthracosis did not show an increase in lymph node size that would suggest malignancy in their follow-up.

The size of the lymph node decreased during the clinical follow-up in one of the three non-diagnostic patients (accepted as having reactive lymph node). The other two patients were diagnosed as malignant via mediastinoscopy (having esophageal CA and squamous cell lung CA). Diagnosis with EBUS-TBNA and the final diagnosis at follow-up are shown in Figure 4. No major complications were observed during the EBUS process or after one week.

The sensitivity was found to be 95.3%, specificity was 100%, the negative predictive value was 97.6%, and the diagnostic accuracy rate was 98.4% in determining the intrathoracic metastases of extrathoracic malignancies in our study.

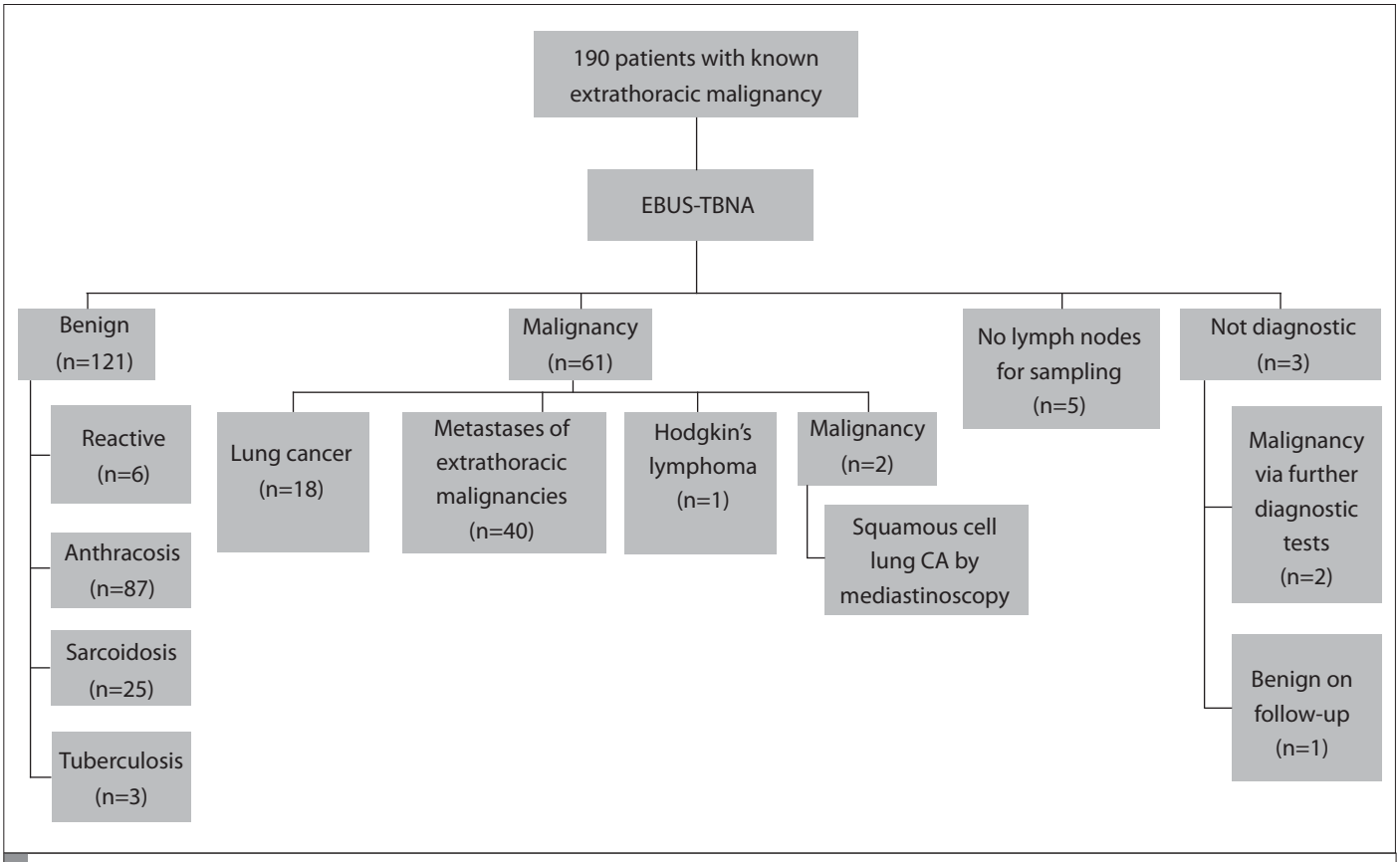

Figure 4. EBUS-TBNA diagnosis, follow-up, and the final diagnosis of patients with extrathoracic malignancy
EBUS-TBNA: endobronchial ultrasound-guided-transbronchial needle aspiration

DISCUSSION

Cancer death rates have been continuously decreasing in the last two decades. Cancer-related deaths in the US decreased by 22% between 1911–2011 (14). This decrease can be explained by the continuing development in cancer treatment. Intrathoracic lymph node metastases in extrathoracic malignancies can be detected earlier by closely monitoring cancer patients. This development is an alternative to mediastinoscopy, and is parallel to the development of EBUS-TBNA and EUS-FNA, which are minimally invasive diagnostic methods (1). Mediastinoscopy has a high risk for the patient and also increases the cost because it requires general anesthesia (6-8). EUS-FNA is a minimally invasive diagnostic method used to evaluate mediastinal lymph nodes in staging (4, 9-10). Accordingly, the sensitivity of EUS-FNA in a series of 75 patients, retrospectively analyzed for detecting the mediastinal metastases of extrathoracic malignancies, was determined as 86%, and the negative predictive value (NPV) was determined as 72% (4); also, in another prospective study on 20 patients, the sensitivity of EUS-FNA was determined as 68% (9). However, while EUS-FNA can only evaluate the left lower paratracheal, aortopulmonary window, subcarinal, and paraesophageal areas, the bilateral hilar and right lower paratracheal areas cannot be sampled.

While EBUS-TBNA is often used for diagnosing mediastinal or hilar lymph nodes and for staging lung cancer, it is also used to diagnose lesions adjacent to the central airways, to detect the depth of tumor invasion of the bronchial wall, and occasionally, to determine central pulmonary embolism (15). Although most studies related to EBUS-TBNA in the early years were on the diagnosis and staging of lung cancer, in the following years, there were more studies reporting that it can also be used for diagnosing sarcoidosis (16).

Nevertheless, there are still a few studies demonstrating the use of EBUS-TBNA in determining the intrathoracic metastases of extrathoracic malignancies (12, 17-20). In a retrospective study including 92 patients, the sensitivity of EBUS-TBNA was 85% (17); a similar study, in which 161 patients were included, found the sensitivity to be 87% and NPV to be 73% (12).

Sanz-Santos et al. (20), in their recently published study that included 117 patients, similarly reported that the sensitivity of EBUS-TBNA in the diagnosis of extrathoracic malignancy with mediastinal metastases was 86.4% and NPV was 75%. In a recently published review, all studies published up to 2014 concerning the value of EBUS-TBNA in determining extrathoracic malignancies with intrathoracic metastases were investigated, and a total of six studies that had a minimum of 30 patients and at least 6 months follow-up were included in the meta-analysis. The sensitivity, specificity, diagnostic sufficiency, and negative likelihood rate of EBUS-TBNA in this meta-analysis were determined as means of 85%, 99%, 85%, and 16%, respectively (13).

In our study, the findings of EBUS-TBNA were examined; 61 patients were malignant, among whom 40 (65.5%) had extrathoracic malignancy-related intrathoracic metastases, 121 were benign, and 3 were not diagnostic. The sensitivity, specificity, NPV, and diagnostic accuracy rate of EBUS-TBNA were much higher at 95%, 100%, 97.6%, and 98.4%, respectively. However, further diagnostic procedures were not applied to patients who were diagnosed as benign by EBUS-TBNA. These patients were followed up

clinically and radiologically for one year; only three patients for whom EBUS-TBNA was non-diagnostic underwent mediastinoscopy. The results obtained in this study were slightly higher than those reported in the literature, and this can be explained as follows: The European Society of Thoracic Surgeons suggests determining whether the patients who underwent pulmonary metastasectomy had lymph node metastases before undergoing surgery. The incidence of lymph node presence in patients undergoing pulmonary metastasectomy was approximately 20% (21). Applying mediastinoscopy to patients is unusual before performing this operation (22). In a study that investigated the availability of mediastinoscopy to this group of patients, metastases were detected in only 10% of the patients (23). Mediastinoscopy is also highly invasive and is a high risk to the patient as it requires general anesthesia, compared to EBUS-TBNA. This result also suggests that EBUS-TBNA should be primarily preferred. Indeed, there are no comparative studies in this field.

There are a few limitations to our work. First, it is a retrospective study. Second, the patients diagnosed with negative malignancy by EBUS-TBNA were followed up clinically/radiologically; advanced histopathological diagnostic techniques were not applied.

In conclusion, EBUS-TBNA, a technique already used in the diagnosis and staging of lung cancer, is a simple, reliable, and adequate diagnostic method for determining intrathoracic lymph node metastases related to known extrathoracic malignancies. EBUS-TBNA can be primarily preferred to determine mediastinal metastases in this group of patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Keçiören Training and Research Hospital.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.Y., A.Ö.; Design - A.Y., A.Ö.; Supervision - A.Y., A.Ö., Z.A.; Resources - A.Ö., A.Y., N.Y.D., Z.A.; Materials - F.D., A.Ö., A.Y.; Data Collection and/or Processing - A.Ö., A.Y., N.Y.D., Z.A.; Analysis and/or Interpretation - A.Ö., A.Y.; Literature Search - A.Ö., A.Y.; Writing Manuscript - A.Ö.; Critical Review - A.Y., A.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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