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## Endobronchial ultrasound-guided transbronchial needle biopsy for the diagnosis of mediastinal lymphadenopathy in patients with extrathoracic malignancies

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**Background/aim:** Mediastinal lymphadenopathy is common in extrathoracic malignancies and should not always be considered a metastatic lesion. The purpose of this study is to determine the diagnostic value of endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNA) in patients with extrathoracic malignancies.

**Materials and methods:** This study included 54 consecutive patients with extrathoracic malignancies who had suspected mediastinal metastases and had undergone EBUS-TBNA for diagnosis.

**Results:** Using EBUS-TBNA, 27 of 54 patients (50%) were diagnosed with mediastinal metastases. Among patients with mediastinal metastases, 2 (3.7%) had a sarcoid-like reaction, 5 (9.3%) had tuberculosis, and 17 (31.5%) had reactive lymph nodes. In 3 cases (5.5%), a specific diagnosis could not be determined following EBUS-TBNA. Two patients underwent surgical staging of their mediastinal lymphadenopathy, which allowed the detection of mediastinal metastases in 1 patient and that of reactive lymph nodes in the other. The sensitivity, specificity, negative predictive value, and diagnostic accuracy of EBUS-TBNA for the diagnosis of extrathoracic malignancies were calculated as 93%, 100%, 92.6%, and 96.3%, respectively.

**Conclusion:** EBUS-TBNA is a safe and effective procedure. We should consider whether EBUS-TBNA should be the primary diagnostic tool for the diagnosis of mediastinal lymphadenopathy in patients with extrathoracic malignancies.

**Key words:** EBUS-TBNA, extrathoracic malignancies, mediastinal lymphadenopathy

### 1. Introduction

Enlarged mediastinal lymph nodes can occur in both intrathoracic and extrathoracic malignancy cases. This frequently poses a diagnostic challenge for respiratory physicians and oncologists.

Intrapulmonary metastatic lesions spread through the vascular system and then form lymph node metastases by lymphatic spread (1). Mediastinal lymphadenopathy that is detected during follow-up visits for patients with extrathoracic malignancies should not always be considered a metastatic lesion. Instead, it could be a simultaneous primary lung malignancy or granulomatous disease. Determining the etiology of lymph node status is important for making decisions about therapeutic management and for determining prognosis (2).

Breast carcinoma, colorectal carcinoma, renal cell carcinoma, and melanoma are all prone to spreading to the chest. Computed tomography (CT) scans are commonly used to diagnose lung metastases. Identification of lymph node metastasis is more problematic since a metastasis

with an upper size limit of 4 mm may result in a false negative rate of approximately 10% by CT (3). Positron emission tomography (PET)-CT images display signs that can help the physician to differentiate between benign and malignant disease, making this an important method for the evaluation of mediastinal lymphadenopathy.

However, inflammatory reactions of lymph nodes may lead to the accumulation of fluorodeoxyglucose (FDG), resulting in a 10% false positive rate. False positive PET results may confuse clinicians; therefore, histopathological confirmation is required (4). For many years, mediastinoscopy has been the most commonly used technique for sampling intrathoracic lymphadenopathy. However, it only has limited usefulness for the evaluation of the aorticopulmonary window and the posterior subcarinal and hilar regions. Furthermore, mediastinoscopy requires general anesthesia, and patients receiving chemotherapy may be reluctant to undergo this invasive procedure (5,6). Endobronchial ultrasound (EBUS), which only requires conscious sedation, is a more easily applicable technique

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and is less expensive than mediastinoscopy. Moreover, EBUS allows sampling from the posterior subcarinal and hilar regions. For these reasons, over the last few years clinicians have been implementing EBUS for the evaluation of mediastinal lymph nodes.

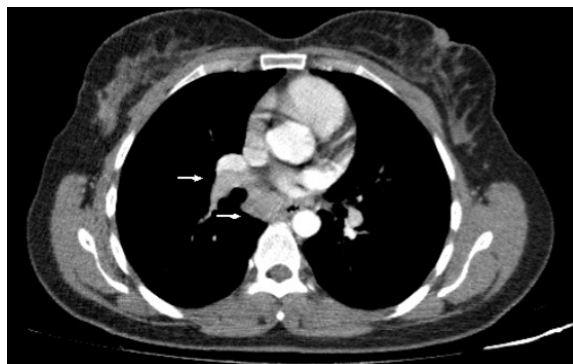
EBUS with real-time guided transbronchial fine-needle aspiration (TBNA) is currently used as a reliable diagnostic tool for enlarged lymph nodes in patients with malignancies, as well as for the evaluation of suspected benign granulomatous diseases. Studies show that this method has high specificity and accuracy but low negative predictive value (NPV) and sensitivity, which necessitates a confirmatory technique in the case of a nonmalignant result from EBUS-TBNA of a suspicious mediastinal lymph node (7).

The aim of this study is to determine the diagnostic value of EBUS-TBNA for mediastinal lymphadenopathy in patients with extrathoracic malignancies. The accurate diagnosis of lymph node metastasis is very important for deciding which treatment modality is chosen. Therefore, EBUS-TBNA should be applied in order to assess lymph node metastasis before mediastinoscopy.

## 2. Materials and methods

Fifty-four consecutive patients, who were suspected to have intrathoracic lymph node metastasis resulting from extrathoracic malignancies between 2010 and 2012 and who had undergone EBUS-TBNA, were retrospectively reviewed (7.5 MHz, BF-UC160F; Olympus Optical Co., Tokyo, Japan). Written informed consent was obtained from all patients and the study was approved by the local institutional ethics committee.

All EBUS-TBNA procedures were performed under moderate sedation with intravenous midazolam alone, or midazolam plus fentanyl, by the same interventional pulmonologist. Patients were suspected to have intrathoracic lymph node metastases based on enlargement (short axis of >10 mm) visualized by CT or FDG uptake of  $\geq$ SUV 2.5 on PET scans (Figure 1). Before EBUS-TBNA, a pulmonologist used flexible bronchoscopy to examine each patient. No endobronchial mucosal abnormalities were found. EBUS-TBNA was subsequently used to examine all accessible lymph nodes. At least 3 passes were performed in each lymph node (Figure 2). A portion of the needle sample was spread on glass slides and dried at room temperature for Ehrlich–Ziehl–Neelsen staining and cytological examination. Another sample portion was placed in a mixture of alcohol and formaldehyde. Separate samples were also put in formaldehyde to form cell blocks and were cultured in Löwenstein–Jensen medium. The remaining material was put in a saline solution and sent to a molecular laboratory for assessment of the presence of tuberculosis by polymerase chain reaction.



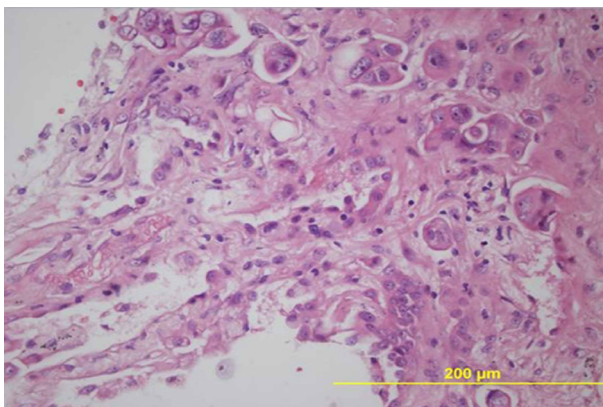
**Figure 1.** Thorax CT showing right hilar (11R) and subcarinal (7) lymph node of the patient, performed by EBUS-TBNA.



**Figure 2.** The view of right hilar lymph node (11R) with EBUS showed hyperechogenicity, a pathological breast carcinoma.

Demographic data, sites of primary malignancies, EBUS findings, cytological findings, and final diagnoses were recorded.

Malignant lymph nodes were defined by pathological examination of malignant cells in EBUS-TBNA (Figure 3). Benign lymph nodes were defined by a histological evaluation that showed benign cells without evidence of



**Figure 3.** Cytology obtained by EBUS-TBNA that demonstrates breast cancer.

malignancy. A 1-year follow-up of clinical and imaging examinations was accepted as negative evidence of malignancy. Only 2 patients underwent EBUS-TBNA followed by a mediastinoscopy under general anesthesia.

### 2.1. Statistical analysis

Sensitivity, specificity, and NPV were based on standard definitions, as was diagnostic accuracy. Statistical analysis was carried out with SPSS 20.  $P < 0.05$  was interpreted as significant.

### 3. Results

We reviewed data from 54 consecutive patients that were suspected of having mediastinal or hilar metastasis of a previously known and treated or concurrent extrathoracic malignancy. Twelve patients (22.2%) were suspected to have metastasis from a simultaneous tumor, and 42 patients (77.6%) had a previously diagnosed extrathoracic malignancy. The mean age of the 40 male (66.7%) and 20 female (33.3%) patients was  $59.9 \pm 12.6$  years (range: 24–83 years). A total of 98 lymph nodes were sampled using EBUS-TBNA. No sample was taken from 1 patient. The mean size of the lymph nodes detected by EBUS was 15 mm (range: 5–35 mm). The subcarinal lymph node was assessed in 35 patients (58.3%), making it the most common location for EBUS-TBNA. Nodes were aspirated at least 3 times. When all samples were evaluated, it was found that the sensitivity, specificity, NPV, and diagnostic accuracy of EBUS-TBNA for the diagnosis of extrathoracic malignancies were 93%, 100%, 92.6%, and 96.3%, respectively. No complications occurred during the EBUS-TBNA procedure.

Analysis of the EBUS results revealed malignancy in 27 cases (50%), sarcoidosis in 2 cases (3.7%), tuberculosis in 5 cases (9.3%), and reactive lymph nodes in 17 cases (31.5%). Three patients (5%) did not have a specific diagnosis following EBUS-TBNA. Patient characteristics are presented in Table 1. In this study group, 2 patients underwent mediastinoscopy, which revealed colon carcinoma metastases in 1 patient and led to a diagnosis of reactive adenitis in the other. Surgery was not considered due to the poor general condition of the patient. Two patients demonstrated progressive mediastinal disease radiologically, without histological evidence, and this was accepted as a positive sign of a tumor. Radiological 1-year follow-ups of the remaining cases revealed a significant decrease in lymph node size, on the basis of which they were considered benign. The distribution of patients based on EBUS-TBNA and final diagnosis are shown in Figure 4.

EBUS-TBNA findings were positive for signs of malignancy in 27 of 54 patients (50%). Eight of these 33 patients were diagnosed with a cancer different from their previous diagnosis: 2 colon cancers, 2 lymphomas, 1 breast cancer, 1 liver cancer, 1 bladder cancer, and 1 stomach cancer (Table 2).

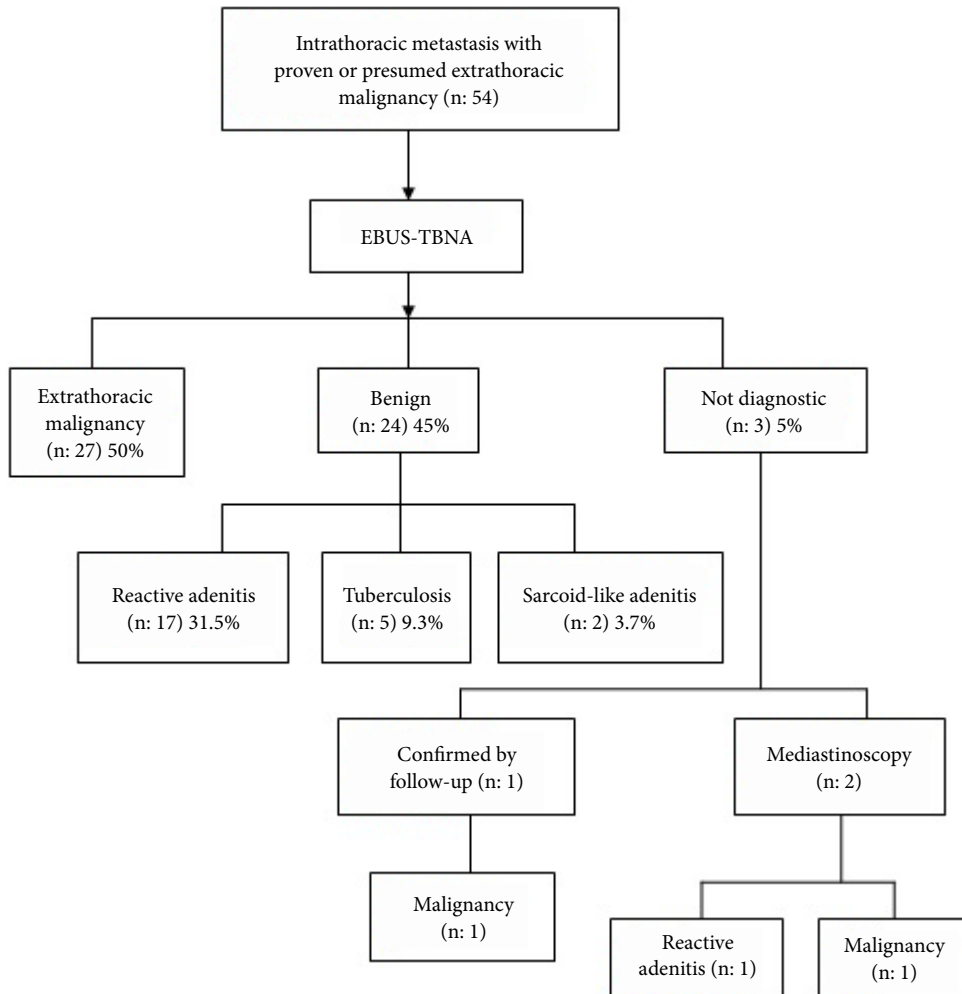
### 4. Discussion

In this study we found that, while 27 of 54 patients (50%) were positive for malignancy, 24 (45%) had a benign condition and 3 (5%) could not be diagnosed. It was also found that the sensitivity, specificity, NPV, and diagnostic accuracy of EBUS-TBNA for the diagnosis of

**Table 1.** Characteristics of the study population.

	Frequency (n)	Percentage (%)
No. of patients	54	
Male/female	35/19	64.8/35.2
Median age in years (range)	60 (24–83)	
Size of mediastinal LNs	15 (5–35)	
Concurrent extrathoracic malignancy	12	22.2
Previous extrathoracic malignancy	42	77.8
Metastasis of extrathoracic malignancy	27	50
Benign results from EBUS-TBNA	24	45

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle biopsy, LNs: lymph nodes.



**Figure 4.** The flow chart of patients enrolled in the study.

extrathoracic malignancies were 93%, 100%, 92.6%, and 96.3%, respectively.

Mediastinal lymphadenopathy is common in the course of extrathoracic malignancies. Up to 30% of extrathoracic malignancies could lead to metastasis of the mediastinum. A frequent metastatic pathway to the thoracic lymph nodes is a lymphatic spread from an intrapulmonary metastatic lesion that occurs by vascular spread (8,9).

A treatment strategy has not been established for these cases, and it is difficult to predict patient prognosis in cases involving mediastinal lymph node spread. Enlarged lymph nodes at the base of the malignancy are not always considered as a malignancy, nor as a pioneer of metastasis. Postobstructive pneumonia, sarcoidosis, and tuberculosis can also be associated with inflammation. Moreover, they may coincidentally be found in primary lung cancer. For this reason, a pathological examination should be conducted to confirm the diagnosis.

Imaging techniques with high sensitivity and specificity are needed to replace invasive staging methods and still arrive at a correct diagnosis. EBUS and/or endoscopic ultrasound (EUS) should be the preferred methods for patients with poor performance status, as they are less invasive and do not require general anesthesia (7).

EUS-fine-needle aspiration (FNA) is an accurate and minimally invasive mediastinal staging procedure for patients with extrathoracic malignancies and is also a promising alternative to surgical staging. However, EUS-FNA has limited ability to target nodes located at the right lateral trachea or hilar and interlobar lesions. EBUS, however, allows the assessment of these lymph nodes (10).

Sampling of mediastinal and hilar lymph nodes by EBUS-TBNA is one of the key procedures in lung cancer staging. EBUS-TBNA can be used to detect all lymph node stations and also allows access to the posterior subcarinal and hilar lymph nodes. Another advantage of EBUS-

**Table 2.** Histopathological diagnosis of 54 patients with extrathoracic malignancy undergoing EBUS-TBNA for diagnosis of intrathoracic nodal metastases.

EBUS-TBNA results	No.	Final diagnosis	Frequency (n)	Percentage (%)
Malignant	27	Laryngeal carcinoma	2	3.7
		Breast carcinoma	4	7.5
		Bladder carcinoma	3	5.6
		Lymphoma	8	14.8
		Colon carcinoma	2	3.7
		Prostate carcinoma	2	3.7
		Esophageal carcinoma	2	3.7
		Sarcoma	2	3.7
		Malignant melanoma	2	3.7
Benign	24	Tuberculosis	5	9.2
		Sarcoidosis	2	3.7
EBUS-TBNA results not diagnostic	3	Reactive adenitis	17	31.5
		Colon carcinoma	2	3.7
		Reactive adenitis	1	1.8
		Total	54	100

EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle biopsy.

TBNA is that it is less expensive than mediastinoscopy.

Herth et al. assessed EBUS-TBNA in patients with lung cancer that had radiographically normal mediastina, and they unexpectedly detected mediastinal metastasis sized 5–10 mm in 17% of the patients. In one patient, EBUS helped doctors avoid a futile thoracotomy (11).

In another study conducted in the same period, EBUS-TBNA was used to sample 163 lymph nodes from 105 patients, and the sensitivity, specificity, positive diagnostic value, negative diagnostic value, and rate of accuracy diagnosis were found to be 94.6%, 100%, 100%, 89.5%, and 96.3%, respectively. By using EBUS-TBNA, doctors were able to avoid unnecessary procedures such as mediastinoscopy (29 patients), thoracotomy (8 patients), thoracoscopy (4 patients), and transthoracic needle aspiration-guided CT biopsy (9 patients) (12).

A recent study compared EBUS-TBNA and mediastinoscopy. It found that the sensitivity, NPV, and diagnostic rates for EBUS-TBNA were 81%, 91%, and 93%, respectively, and 79%, 90%, and 93%, respectively, for mediastinoscopy (13). There are cases where the imaging evaluation of the mediastinum is not sufficient. Therefore, EBUS-TBNA is recommended even for patients without

visible lymphadenopathy by thoracic CT and PET-CT during the preoperative period. This is a less invasive method with a shorter recovery time than surgical staging (14).

Six articles in the medical literature have reported on the ability of EBUS to detect intrathoracic metastasis of extrathoracic malignancies. The first to address the diagnostic value of EBUS-TBNA for mediastinal involvement of extrathoracic malignancies indicated a high yield and safety for this procedure. It also considered the impact of this procedure on patient management. EBUS-TBNA was used in 92 cases, and in 52 of these cases (57%) mediastinal or hilar metastatic spread was detected. The sensitivity and NPV were calculated as 85% and 76%, respectively (15).

Due to the low NPV, negative tumor findings should be verified by surgical techniques. EBUS is a good test to demonstrate mediastinal metastatic involvement, but a negative result from EBUS does not preclude mediastinal metastasis (11). In the present study, the NPV of EBUS-TBNA for the diagnosis of extrathoracic malignancies was found to be 92.6%. The results of the present study were in agreement with those of Yasufuku et al. (12).



Similarly, in 2011, Park et al. reported encouraging results for EBUS-TBNA, which gave a sensitivity and specificity for the detection of mediastinal malignancies in patients with previous extrathoracic malignancies of 93.3% and 100%, respectively. In patients without a previously diagnosed malignancy, these values were 61.5% and 100%, respectively. The overall sensitivity and specificity of EBUS-TBNA was found to be 81.0% and 100%, respectively (16).

Subsequently, Navani et al. reported the results of a multicenter study in which 161 patients with extrathoracic malignancies with intrathoracic lymph node metastases were evaluated by EBUS-TBNA. EBUS-TBNA had a sensitivity of 87%, NPV of 73%, and overall accuracy of 88%. This study reported that EBUS-TBNA diagnosed mediastinal and/or hilar metastases in 44% of patients, new lung cancer in 12% of patients, and sarcoidosis in 9% of patients (17).

Parmaksız et al. analyzed 48 cases of confirmed extrapulmonary malignancies, and only 18 patients (37.5%) were found to have a metastasis. The most important finding of their study was the high prevalence of benign conditions, which showed that in 10 patients (20.8%), EBUS-TBNA demonstrated the presence of granulomatous diseases. They proposed that definitive tissue evaluation is necessary to diagnose nodal metastasis (18).

In this study, which included 54 patients with extrathoracic malignancies and suspected metastasis, we found that only 27 patients (50%) had a final diagnosis of intrathoracic lymph node metastasis, and 24 patients (45%) were confirmed as having benign disease. Granulomas were found in 7 patients. Five of these patients had tuberculosis and 2 showed a sarcoid-like reaction.

The histopathological analysis of various extrathoracic malignancies might be more difficult when compared to lung cancer samples. Cytopathologists are aided in their analysis by immunohistochemical staining on cell-block preparations. Recently, Santos et al. reported that EBUS-TBNA can be used to diagnose thoracic lymph node metastasis from extrathoracic malignancies with a sensitivity and NPV similar to previous studies. Moreover, in their cohort of 117 patients, the use of EBUS-TBNA avoided invasive surgical diagnostic procedures and allowed immunohistochemical staining, which was performed for 80.4% of the samples. In this study, EBUS-TBNA could be used to obtain specimens from all patients

with suspected metastasis, allowing supporting studies to be undertaken, such as immunohistochemical staining on cell-block preparations (19).

The development of an underlying malignancy in a patient without symptoms or signs suggests systemic sarcoidosis, and this is often referred to as a sarcoid-like reaction. The hypermetabolic hilar and mediastinal lymph nodes were the result of a sarcoid-like reaction.

It has been estimated that 4%–14% of all patients with cancer exhibit histopathologic evidence of a sarcoid-like reaction, and it has been described in association with different tumor types. This reaction is especially common in squamous cell carcinomas (20,21).

In the present study, 2 patients with noncaseating granulomas were detected by EBUS-TBNA. In both cases there was no evidence of cancer or tuberculosis, suggesting a sarcoid-like reaction. These patients had a history of squamous cell carcinoma of the larynx, and no pulmonary symptoms or signs were found that were suggestive of systemic sarcoidosis. Furthermore, 1 year of clinical and imaging follow-up has revealed no evidence of malignancy or systemic sarcoidosis. These findings are consistent with previous studies.

This study has a number of limitations. First, we collected data retrospectively. Second, this study included only a small number of patients from a single center. We could not use mediastinoscopy for all patients who had a negative EBUS-TBNA result, as this was prevented by protocol due to ethical considerations.

This study suggests that enlarged and hypermetabolic mediastinal and hilar lymph nodes develop into different types of malignant and benign conditions. Because most diseases show differences in prognosis and treatment methods, physicians should use EBUS-TBNA to distinguish primary lung cancer from benign conditions. Pathological evaluation is mandatory for the diagnosis and staging of patients with extrathoracic malignancies. EBUS-TBNA should be used in cases of patients with poor health and significant comorbidities, and this method should be considered as the primary test for pathological evaluation.

In conclusion, our findings indicate that EBUS-TBNA is a safe, minimally invasive, and effective procedure for the diagnosis of thoracic lymph node metastases in patients with concurrent or previously diagnosed extrathoracic malignancies. The procedure can be considered as an initial diagnostic technique for these patients.

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