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The utility of EBUS-TBNA in mediastinal or hilar lymph node evaluation in extrapulmonary malignancy

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Background/aim: The aim of this study was to determine the diagnostic performance of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of mediastinal and hilar lymph nodes (LNs) in patients with known extrapulmonary malignancy.

Materials and methods: Between March 2011 and August 2013, 378 EBUS-TBNA procedures were performed. Sixty-three (16.6%) of these were performed on known extrapulmonary malignancy patients.

Results: There were 28 male and 35 female patients, with median ages of 65 years (min–max: 53–87) and 57 years (min–max: 39–76), respectively. From the 63 cases, 138 lymph nodes (LNs) were sampled with EBUS-TBNA (median: 2 LNs/patient; min–max: 1–4). Results of EBUS-TBNA revealed malignancy in 18 (28.5%) and nonmalignancy in 45 (71.5%). In the nonmalignant group, there were false negatives in 5 (7.9%), anthracosis in 13 (20.6%), reactive adenitis in 16 (25.3%), sarcoidosis in 7 (11.1%), and tuberculosis in 2 (3.1%), and 2 were not evaluated (lost to follow-up) (3.1%). The diagnostic sensitivity, accuracy, and negative predictive value of EBUS-TBNA per patient were 78.2%, 91.8%, and 88.3%, respectively.

Conclusion: EBUS-TBNA is a safe, minimally invasive, and effective method and can be considered as the initial test for the histopathological diagnosis of mediastinal and hilar lymphadenopathy in patients with extrapulmonary malignancy.

Key words: Endobronchial ultrasound-guided transbronchial needle aspiration, extrapulmonary malignancy, lymph node, mediastinum, metastasis

1. Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive and safe procedure that allows the bronchoscopist to see beyond the airway and to evaluate the diagnostic possibilities for mediastinal and hilar pathology. There are many reports confirming the diagnostic accuracy and safety of EBUS-TBNA for nodal staging of nonsmall-cell lung cancer (1–5). Mediastinal and hilar lymphadenopathy do not always result from cancer; granulomatous diseases and pneumoconiosis can be the causes of mediastinal or hilar lymphadenopathy (6). The diagnosis of mediastinal and hilar lymphadenopathy is important for the prognosis and further treatment plan in patients with extrapulmonary malignancy. Therefore, histopathological confirmation of mediastinal lymphadenopathy is required.

Imaging studies, including computed tomography (CT) and positron emission tomography (PET), are currently available for detection of mediastinal metastases. However, these modalities are often regarded as insufficient for making a clinical decision because they do not allow pathologic confirmation (4,7). Invasive procedures may be needed for a definitive diagnosis. Although mediastinoscopy remains the gold standard for evaluation of the mediastinum, it requires general anesthesia and is associated with higher morbidity and mortality, in addition to the fact that it cannot be used to evaluate the hilar lymph nodes.

Recently, the utility of EBUS-TBNA for the evaluation of mediastinal lymphadenopathy in lung cancer staging (1–5), sarcoidosis (8–10), tuberculosis (11,12), or lymphoma (13,14) has been reported. However, the role of EBUS-TBNA in the diagnosis of mediastinal or hilar metastasis from extrapulmonary malignancy has not been well established, despite the results of recent studies (15–19). Therefore, our primary endpoint was to determine the etiology and prevalence of malignancy for hypermetabolic or enlarged hilar/mediastinal lymph nodes (LNs) in patients with a previously diagnosed extrapulmonary malignancy during the oncologic follow-up period, and the diagnostic yield of EBUS-TBNA in these LNs.

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2. Materials and methods

2.1. Patients

This retrospective study was conducted in a tertiary hospital located in İzmir, which has a surface area of 12,000 km^2 and a population of approximately 4 million, between March 2011 and August 2013. Over the study period, a total of 378 patients underwent EBUS-TBNA for the staging and diagnosis of primary lung cancer, extrapulmonary malignancy, tuberculosis lymphadenitis, sarcoidosis, and a variety of clinical indications. Sixty-three patients with proven or suspicious extrapulmonary malignancy who underwent EBUS-TBNA for the diagnosis of nodal metastasis were included in the study.

Demographic data, sites of primary malignancies, radiological and PET-CT findings, EBUS findings, stations of aspirated LNs, cytological and histological findings and diagnoses, final diagnoses, and procedure-related complications were recorded. Informed consent was obtained from all patients for procedures and the use of medical records.

2.2. Radiological evaluation

The indication of EBUS-TBNA in enrolled patients was a LN with a short-axis diameter of ≥10 mm on thoracic CT and/or LN with 18-fluorodeoxyglucose (FDG) uptake. Patients had PET-CT scans as a part of their routine oncological evaluation. The FDG PET-CT was considered positive if the PET-CT report stated that there was hypermetabolic activity with a standardized uptake value of ≥2.5, consistent with malignant disease.

2.3. The EBUS-TBNA procedure

All EBUS-TBNA procedures were performed by the same bronchoscopist. The EBUS-TBNA procedure was performed by an EBUS-guided TBNA bronchoscope (7.5 MHz, BF-UC160F; Olympus Optical Co., Tokyo, Japan) through the oral route, in the supine position under local anesthesia with lidocaine and conscious sedation with intravenous midazolam. Heart rate and oxygen saturation of all patients were monitored during the procedure. An examination of all mediastinal and hilar lymph node stations accessible by EBUS were performed prior to the TBNA procedure. The lymph node station was determined according to the new international lymph node map proposed by the International Association for the Study of Lung Cancer (20).

If more than one node was detected, the decision of which node to puncture depended on the physician's judgment based on findings from the CT and/or PET/CT scans. Each target nodal station was punctured at least twice, and one or more tissue core specimens were obtained with a dedicated 22-gauge needle (NA-201SX-4022, Olympus). The aspirate was then blown onto a glass slide by pushing air using a 20-mL syringe. Aspirated material was also obtained for cell block and mycobacterial cultures. If no tissue core specimen was obtainable from the initial 2 aspirations, 3 or more aspirations of the lymph node were performed until enough tissue core was obtained.

Serious complications such as respiratory failure, bleeding requiring transfusion, pneumothorax, pneumomediastinum, or any minor complication such as oxygen desaturation or arrhythmia during the procedure were evaluated.

2.4. Pathological examination

Some amount of the aspirate was smeared onto glass slides, air-dried, fixed immediately with 95% alcohol, and stained with hematoxylin and eosin (H&E). The rest of the aspirate was placed into a mixture of formalin and alcohol in order to obtain a cell block for histological examination. Rapid on-site cytological examination was not available.

2.5. Mycobacterial cultivation and identification

Fine-needle aspiration biopsy specimens obtained from patients and placed in sterile tubes were transported to the microbiology laboratory immediately. In the laboratory, the samples were suspended in 1 mL of Middlebrook 7H9 medium and vortexed. The suspensions were then digested and decontaminated by using a commercial decontamination kit, Mycoprosafe (Salubris AS, İstanbul, Turkey). Mycobacterial cultivation was performed by MGIT 960 system (BD Biosciences, Sparks, MD, USA) according to the recommendations of the manufacturer as described elsewhere (21), and in Lowenstein–Jensen slants (Salubris AS). An acid-fast smear preparation by fluorochrome and/or Kinyoun staining was also applied to each processed specimen. Differentiation of *Mycobacterium tuberculosis* and nontuberculous mycobacteria was performed by conventional methods (22) and BD immunochromatographic test (BD Biosciences, Sparks, MD, USA). *M. tuberculosis* H37Ra was used as the control strain in all methods.

2.6. Final diagnosis

2.6.1. Malignancy

EBUS-TBNA results were considered malignant when the aspirated material contained malignant cells. Tumor-positive findings from the EBUS-TBNA samples were not surgically validated.

2.6.2. Granulomatous inflammation

A final diagnosis of sarcoidosis was made in the presence of all of the following criteria: 1) consistent clinical and radiological presentation; 2) demonstration of necrotizing or nonnecrotizing granulomas on EBUS with negative acid-fast bacilli and no growth of mycobacteria on culture; 3) clinical and radiological response after treatment with glucocorticoids or spontaneous remission.

Diagnosis of tuberculosis was based on demonstration of all of the following: granulomatous inflammation

and the presence of acid-fast bacilli on microscopy, or a positive culture for *M. tuberculosis* and clinico-radiological response to antituberculosis treatment.

2.6.3. Anthracotic adenitis

When the presence of compact anthracotic pigment was evaluated by the pathologists during the microscopic examination of aspiration and histological specimens, the LN was accepted as showing anthracotic adenitis.

2.6.4. Reactive adenitis

When the presence of lymphocytes, macrophages, and immunoblasts and no presence of malignant cells, granulomatous inflammation, compact anthracotic pigment, or abundant epithelia cells were evaluated by the pathologists in the microscopic examination of aspiration and histological specimens, the LN was accepted as showing reactive adenitis.

2.6.5. Follow-up

Any diagnosis other than malignancy required further investigation, such as mediastinoscopy or thoracoscopy, or radiologic follow-up on the outcome of the LNs for at least 6 months. At the end of the follow-up period, the LNs that were diagnosed as showing sarcoidosis, tuberculosis, reactive adenitis, or anthracotic adenitis by EBUS-TBNA and were stationary, decreased in size, or disappeared were considered benign.

2.7. Statistical analysis

The statistical analyses were performed using SPSS 20. Data were presented as medians and interquartile ranges (IQRs, 25th and 75th percentiles) for continuous variables and as numbers and percentages for categorical variables. The diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of EBUS-TBNA and PET-CT scan were calculated by standard definitions.

3. Results

3.1. Patient characteristics

All 63 patients (28 male, 35 female) successfully underwent EBUS-TBNA. The median ages of the male and female patients were 65 years (min–max: 53–87) and 57 years (min–max: 39–76), respectively. The most common extrapulmonary malignancies observed were genitourinary carcinoma (26.9%), followed by breast carcinoma (23.8%), gastrointestinal malignancy (23. 8%), and head and neck cancer (17.4%) (Table 1).

3.2. Details related to mediastinal and hilar lymph nodes

All patients had thoracic CT, and 54 patients had PET-CT. One hundred and twenty LNs were hypermetabolic on PET-CT. The frequencies of hilar and mediastinal LNs assessed by EBUS-TBNA are shown in Table 2. A total of 138 LNs were sampled. The median number of LN stations sampled per patient was 2 (IQR: 2–3). The median short-

Table 1. Data for the 63 patients with extrapulmonary malignancy.

Malignancy	N	%
Breast carcinoma	15	23.8
Head and neck cancer	11	17.4
Laryngeal carcinoma	5	7.9
Salivary gland cancer	3	4.7
Nasopharynx carcinoma	2	3.1
Thyroid carcinoma	1	1.5
Genitourinary malignancy	17	26.9
Ovarian carcinoma	4	6.3
Endometrial carcinoma	4	6.3
Prostate cancer	2	3.1
Renal cell carcinoma	5	7.9
Bladder carcinoma	1	1.5
Adrenal liposarcoma	1	1.5
Gastrointestinal malignancy	15	23.8
Gastric carcinoma	6	9.5
Esophageal cancer	1	1.5
Pancreatic carcinoma	2	3.1
Colon	2	3.1
Rectum	4	6.3
Others	5	7.9
Skin	1	1.5
Melanoma	1	1.5
Conjunctiva	1	1.5
Chronic lymphocytic leukemia	2	3.1

Table 2. The frequency of the lymph nodes sampled by EBUS-TBNA.

Lymph node	N (%)
Upper paratracheal lymph node	15 (10.8)
2R	13 (9.4)
2L	2 (1.4)
Lower paratracheal lymph node	43 (31.1)
4R	32 (23.1)
4L	11 (7.9)
Subcarinal lymph node (7)	43 (31.1)
Hilar or interlobar lymph node	37 (26.8)
10R	3 (2.1)
10L	3 (2.1)
11R	17 (12.3)
11L	14 (10.1)

R: Right, L: Left.

axis of aspirated mediastinal LNs was 15 mm (IQR: 10–20 mm). In terms of stations, only hilar (stations 10 or 11) nodes in 3 (4.7%) patients, only mediastinal (stations 2, 4, 7) nodes in 29 (46%) patients, and both hilar and mediastinal nodes in 31 (49.2%) patients were sampled.

3.3. Final diagnostic results

In 18 (28.5%) patients, EBUS-TBNA confirmed metastasis of extrapulmonary malignancy. The EBUS-TBNA results of the remaining 45 cases were reactive lymph adenitis (n = 19), anthracotic lymph adenitis (n = 16), or granulomatous inflammation (n = 10). Mediastinoscopy was performed in 20 of 45 patients. Mediastinal lymph node metastasis (n = 5), reactive adenitis (n = 9), anthracotic lymph node (n = 5), and granulomatous inflammation (n = 1; final diagnosis: sarcoidosis) were diagnosed in patients who underwent mediastinoscopy. The results of false-negative EBUS were 2 anthracosis and 3 reactive lymphadenitis. The extrapulmonary malignancy of these 5 patients were breast cancer, ovarian cancer, laryngeal cancer, endometrial cancer, and parotid cancer.

The diagnostic algorithm for patients with suspected mediastinal and/or hilar metastasis from extrapulmonary malignancy is shown in the Figure. Two patients with nonmalignant EBUS-TBNA results were lost to follow-up. Fifteen patients with a cytological diagnosis of reactive lymph node or anthracosis were followed for a median of 10 (min–max: 6–12) months. Radiological LNs were stable during this period, and these LNs were accepted as the benign results of the EBUS-TBNA procedure.

Of 63 patients, the diagnoses were 23 malignancy (36.5%), 16 reactive lymph adenitis (25.3%), 13 anthracosis (20.6%), 7 sarcoidosis (11.1%), 2 tuberculosis (6.6%), and 2 lost to follow-up. EBUS-TBNA cultures were positive in 2 of the tuberculosis patients. The other 61 patients had a negative culture for *M. tuberculosis*.

3.4. Diagnostic performances

Fifty-four patients had PET-CT and they had 120 LNs on PET-CT. Of 54 patients, the diagnosis were 20 malignancy (37%), 14 reactive lymph adenitis (25.9%), 12 anthracosis (22.2%), 6 sarcoidosis (11.1%), and 2 tuberculosis (3.7%).

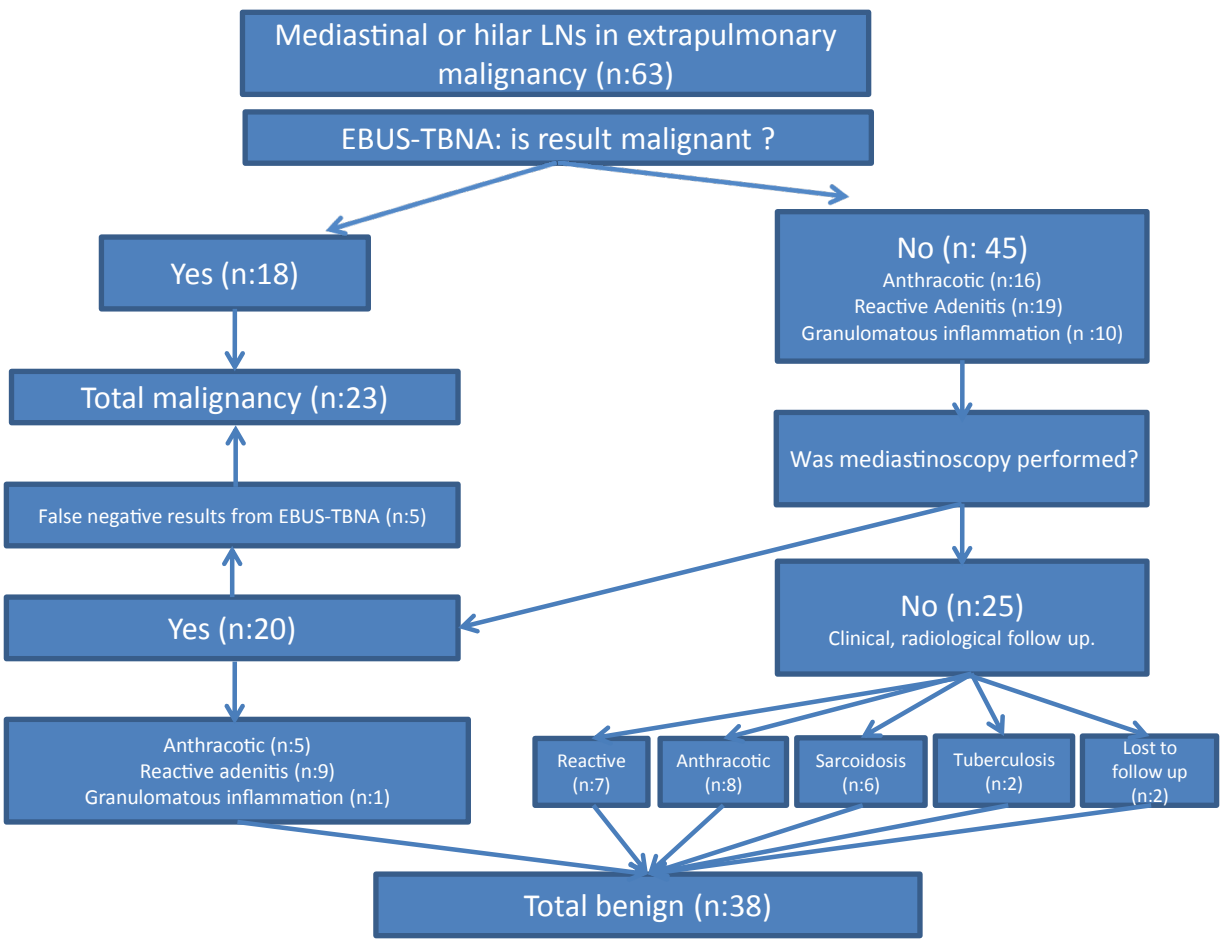

Figure. Diagnostic algorithm for patients with suspected mediastinal and/or hilar metastasis from extrapulmonary malignancy. LNs: lymph nodes; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration.

The diagnostic sensitivity, specificity, PPV, NPV, and accuracy of PET-CT per patient were 85%, 29.4%, 42.8%, 83.3%, and 51.8%, respectively. The diagnostic sensitivity, specificity, PPV, NPV, and accuracy of EBUS-TBNA per patient were 78.2%, 100%, 100%, 88.3%, and 91.8%, respectively (Table 3).

3.5. Complications

Procedure-related complications were minor bleeding in 1 case and slight reversible oxygen desaturation in 1 case. No other serious complications such as pneumothorax or respiratory failure were observed.

4. Discussion

The present study showed that EBUS-TBNA is a sensitive, accurate, minimally invasive, and safe procedure for the evaluation of nodal metastases from extrapulmonary malignancy. EBUS-TBNA demonstrated a sensitivity of 78.2% with an overall diagnostic accuracy of 91.8%; therefore, it is an important alternative to other techniques for the diagnosis of intrathoracic lymphadenopathy in patients with extrapulmonary malignancy.

In particular, the detection of enlarged mediastinal lymphadenopathy in patients with extrapulmonary malignancy is important for the planning of further treatment. Although mediastinoscopy is considered the gold standard diagnostic technique, it is associated with risks due to general anesthesia, a serious complication rate of 1%, and increased healthcare costs when compared with minimally invasive techniques. Moreover, it is limited in accessing the aortopulmonary window and posterior subcarinal and hilar regions.

On the other hand, EBUS-TBNA is an established procedure for sampling mediastinal lymph nodes and is a minimally invasive technique. Earlier studies in mediastinal staging or restaging of nonsmall-cell lung cancer showed high diagnostic rates for EBUS-TBNA, with sensitivity and PPVs of more than 90% and specificity of 100% (3,23,24). Recently, EBUS-TBNA was performed to evaluate intrathoracic lymphadenopathy in patients with extrapulmonary malignancy. A large study of 161 suspected metastases from extrapulmonary malignancy patients undergoing EBUS-TBNA demonstrated a sensitivity rate of 87% (20). Other studies also showed a sensitivity rate of 85%–96.3% (15–18) (Table 4). In the present study, the sensitivity of EBUS-TBNA in suspected metastases from extrapulmonary malignancy patients was 78.2%, which is lower than in other studies. This is because the 3 patients who produced false negative results from EBUS-TBNA were among the first 100 patients. This result may be related to the level of experience of the person who performed EBUS-TBNA. The European Respiratory Society and American Thoracic Society Joint Statement on Interventional Pulmonology states that trainees should perform at least 40 procedures in a supervised setting, and 25 procedures should be done annually to maintain competency. The authors think that the clinician's experience of conventional TBNA seems to be a factor in the EBUS learning period (25). Bizekis et al. found that diagnostic accuracy was better in the last 26 patients than in the first 25 patients. Hence, according to their study, the lowest number of repetitions to learn the procedure was approximately 50 (26).

Moreover, rapid on-site evaluation was not available in our study. Additionally, NPV was 88.3% in this study, which was similar to the results of other studies that reported rates of between 76% and 86.9% (17,19,27,28). Five cases were diagnosed as malignancy after mediastinoscopy, although EBUS-TBNA results were reported as benign. Therefore, the negative results by EBUS-TBNA should be verified by surgical methods if the probability of malignancy is different from clinical and radiological results.

Table 3. Diagnostic performances of F-18 fluorodeoxyglucose positron emission tomography/computed tomography and endobronchial ultrasound-guided transbronchial needle aspiration.

Per patient basis	PET-CT %	EBUS-TBNA %
Sensitivity	85	78.2%
Specificity	29.4	100%
Positive predictive value	42.8	100%
Negative predictive value	83.3	88.3%
Diagnostic accuracy	51.8	91.8%

PET-CT: Fluorodeoxyglucose positron emission tomography/computed tomography.
EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration.

Table 4. Diagnostic performances in the literature and our results.

Study/country	No. of patients	Sensitivity	Specificity	NPV	Accuracy
Song et al., 2011 (17), Korea	56	88%	-	85%	93%
Park et al., 2011 (15), Korea	59	81%	100%	-	-
Navani et al., 2011 (19), UK	161	87%	-	73%	88%
Tournoy et al., 2011 (18), Belgium	92	85%	-	76%	-
Parmaksiz et al., 2012 (27), Turkey	48	89.2%	100%	86.9%	93.7%
Özgül et al., 2013 (16), Turkey	40	90%	100%	90.9%	95%
Sanz-Santos et al., 2013 (28), Spain	117	86.4%	-	75%	90.3%
Our study, 2014, Turkey	63	78.2%	100%	88.3%	91.8%

NPV: Negative predictive value.

Similar to previous studies, our study confirmed that not all enlarged or hypermetabolic LNs in cancer patients are malignant (11,16–19). Of note in the present study are the low specificity (29.4%) and PPV (42.8%) of FDG PET-CT, which need to be discussed. Özgül et al. found that the diagnostic sensitivity, specificity, PPV, NPV, and accuracy of PET-CT scan based on the number of patients were 94.7%, 35.7%, 66.6%, 83.3%, and 69.6%, respectively (16). Song et al. investigated the diagnostic value of EBUS-TBNA and PET-CT in patients with extrapulmonary malignancy. They reported that PET-CT specificity and PPV were both 89%, which was higher than in our study (17). However, it should be noted that FDG is not a cancer-specific diagnostic method; thus, false positive findings in benign diseases have been reported (29,30). Infectious diseases (mycobacterial, fungal, bacterial infection), sarcoidosis, radiation pneumonitis, and postoperative surgical conditions have shown intense uptake on PET scans (30). In addition, pneumoconiosis, such as anthracosis, shows hypermetabolic activity in FDG PET-CT. In developing countries like ours, anthracosis may be another cause of mediastinal lymphadenopathy (31). Our country, Turkey, is one of the countries where granulomatous diseases such as sarcoidosis and tuberculosis are common. In addition, anthracosis associated with biomass exposure or intense smoking is also not rare and should not be forgotten in the differential diagnosis of enlarged hypermetabolic lymph nodes. Therefore, histopathologic confirmation for mediastinal or hilar lymphadenopathy is mandatory in patients with proven or suspected extrapulmonary malignancy, because reliance solely on radiographic findings is insufficient for making an accurate clinical diagnosis. In the present study, we had mostly benign diseases; this caused false positive FDG uptake in PET-CT, which led to a low specificity and a PPV.

There are some limitations of our study. The first major limitation is that this study was a retrospective study performed on a small number of patients from a single center. Second, our population was heterogeneous regarding types of malignancies and the locations of the lymphadenopathy. Benign EBUS-TBNA results were not confirmed with mediastinoscopy. However, the study's strength was that all cases (except 2) were followed clinically and radiologically for at least 6 months.

In conclusion, EBUS-TBNA is a simple, safe, minimally invasive, and accurate procedure for the diagnosis of thoracic lymph node metastases in patients with a known extrapulmonary malignancy. Our findings lead us to recommend the use of EBUS-TBNA as an initial diagnostic technique in these patients. Nevertheless, due to the possibility of underdiagnosis, an invasive technique is indicated when the results are negative.

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