Role of Real-Time Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Diagnosis and Mediastinal Staging of Lung Cancer

Akciğer Kanserinin Teşhisinde ve Mediastinal Evrelemesinde Eş Zamanlı Endobronşiyal Ultrason Kılavuzlu Transbronşiyal İğne Aspirasyonunun Rolü

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ABSTRACT Objective: Real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive new diagnostic tool used for diagnosis and mediastinal staging of lung cancer. The aim of this study is to evaluate the role of real-time EBUS-TBNA for diagnosis of lymph nodes in patients with suspected lung cancer who had mediastinal and/or hilar lymph nodes. **Material and Methods:** Between April 2009 and January 2011, 52 patients with mediastinal and/or hilar lymphadenopathy suspected for lung cancer referred for TBNA were enrolled in the study. **Results:** Of 97 lymph node biopsy specimens, 94 were eligible for diagnosis. Of three patients with malignancy negative lymph node biopsy specimens, two gave their consents and underwent mediastinoscopy. The result of one patient was negative, and the other one was positive for malignancy. The third patient was accepted to have a non malignant disease since the positron emission tomography of lymph node was negative for malignancy and remained stable and non-malignant during the follow-up. The sensitivity and specificity of EBUS-TBNA in the diagnostic evaluation of mediastinal and/or hilar lymph nodes of patients with suspected for lung cancer were 98.9% and 100%, respectively. Twelve N3 lymph nodes were diagnosed as positive for malignancy. Twenty three patients without endobronchial lesions on conventional bronchoscopy were diagnosed as lung cancer by real-time EBUS-TBNA. No complications were recorded during the procedures. **Conclusion:** Real-time EBUS-TBNA is an effective and reliable diagnostic procedure. Moreover, it is a very useful tool for diagnosis of lesions which cannot be reached with the conventional bronchoscope.

Key Words: Lung neoplasms; lymph nodes; diagnosis

ÖZET Amaç: Eş zamanlı endobronşiyal ultrason kılavuzlu transbronşiyal iğne aspirasyonu (EBUS-TBNA) akciğer kanserinin teşhisi ve mediastinal evrelemesi için kullanılıp minimal invaziv olan yeni bir teşhis yöntemidir. Bu çalışmanın amacı akciğer kanseri olarak şüphelenilen ve mediastinal ve/veya hiler lenf nodları olan hastalarda lenf nodlarının teşhisi için eş zamanlı EBUS-TBNA'nın rolünü değerlendirmektir. **Gereç ve Yöntemler:** Nisan 2010-Ocak 2011 arasında akciğer kanseri şüphesi ve mediastinal ve/veya hiler lenf nodları nedeniyle transbronşial biyopsi önerilen 52 hasta çalışmaya alındı. **Bulgular:** Doksan yedi lenf nodu biyopsi örneğinden 94'ü teşhis için uygundu. Lenf nodu biyopsi örneği malignite negatif olarak raporlanan üç hastanın ikisine rıza göstermeleri üzerine mediastinoskopi uygulandı. Bunlardan biri malignite pozitifti. Üçüncü hasta lenf nodunun pozitron emisyon tomografisinin malignensi için negatif olmasından dolayı non-malign olarak kabul edildi ve takip boyunca stabil ve non-malign olarak kaldı. Akciğer kanseri için şüphelenilen hastaların mediastinal ve/veya hiler lenf nodlarının tanısal değerlendirilmesinde EBUS-TBNA'nın özgünlüğü ve özgüllüğü sırası ile %98,9 ve %100 idi. On iki N3 lenf nodu, malignensi için pozitif olarak teşhis edildi. Konvansiyonel bronkoskopiyle endobronşiyal lezyonu olmayan 23 hasta eş zamanlı EBUS-TBNA ile akciğer kanseri olarak teşhis edildi. Genel olarak işlem boyunca herhangi bir komplikasyon kaydedilmedi. **Sonuç:** Eş zamanlı EBUS-TBNA etkili ve güvenilir bir tanısal işlemdir. Daha da ötesi, konvansiyonel bronkoskopi ile ulaşılamayan lezyonların teşhisi için faydalı bir araçtır.

Anahtar Kelimeler: Akciğer tümörleri; lenf nodları; tanı

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The evaluation of mediastinal lymph nodes and masses is important for both diagnostic purposes and lung cancer staging. Imaging methods, such as computed tomography (CT) and positron emission tomography (PET) indicate the size and metabolic activity of mediastinal nodes with a sensitivity and specificity of 57-82% (CT) and 84-89% (PET), respectively.[1,2]

Bronchoscopy plays an important role in the diagnosis and staging. Endobronchial biopsy under direct visualization can provide a diagnosis in more than 90% of cases. However, the majority of lung cancer patients present with primary lesions outside the direct view of the bronchoscope, and the yield of transbronchial needle aspiration for sampling the mediastinum varies widely. In a meta-analysis by Holty and coworkers, the pooled sensitivity for transbronchial needle aspiration (TBNA) mediastinal staging was 39% (95%CI, 17-61%), and the pooled specificity was 99% (95%CI, 96-100).[3] The view from a bronchoscope is limited to the lumen and the internal surface of the airways; thus, expanding the bronchoscopist's view beyond the airway could vastly improve the diagnostic capabilities of diagnostic bronchoscopy.

Surgical staging by mediastinoscopy has a high sensitivity (81%) and specificity (100%).[4] However; it is an invasive procedure that requires general anesthesia and clinical admission.

Endoscopic techniques provide a minimally invasive alternative for surgical staging. Real-time (convex probe) endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a highly accurate and safe method for sampling enlarged mediastinal and/or hilar lymph nodes.[5-13]

The aim of this study is to determine the diagnostic value of real-time EBUS-TBNA in the diagnosis of mediastinal and/or hilar lymph nodes of patients suspected for lung cancer.

MATERIAL AND METHODS

Between April 2009 and January 2011, 52 patients with mediastinal and/or hilar lymphadenopathy suspected for lung cancer referred for TBNA were enrolled in the study. the major indication for TBNA was the need for sampling and diagnosis of enlarged lymph nodes to serve for lung cancer staging, especially the exclusion of N3 cases.

The study subjects and prospective data collection was done in the Chest Diseases Department of Eskisehir Osmangazi University Medical School, where all patients were examined by the authors. The study protocol was approved by the Ethics Committee of Eskisehir Osmangazi University Medical School, and all participants provided their written informed consents.

Chest radiography and CT scan of chest were routinely performed in all patients. A lymph node was considered to be enlarged if its short-axis diameter was >1 cm.

Conventional flexible bronchoscopy (Model 1T-60 bronchoscope; Olympus, Tokyo, Japan) was first performed as a standard procedure to examine the tracheobronchial tree, followed by TBNA using real-time EBUS bronchoscopy (Model XBF-UC160F-OL8; Olympus, Tokyo, Japan). Both bronchoscopy procedures were performed by the same bronchoscopist, under local anesthesia and sedation with midazolam. Patients in whom a specific diagnosis was not determined by biopsy specimens obtained with EBUS-TBNA underwent a surgical biopsy procedure.

EBUS-TBNA

Real-time EBUS bronchoscope was passed through the month and vocal cords into the carina. The balloon, if used, was partially inflated and the regional lymph node stations of the mediastinum and/or hilar regions (station 2,4,7,10,11) were systematically viewed and measured (short-axis diameter) during slow withdrawal and rotation of the transducer. Each target nodal station was aspirated three times with a fine 22 gauge needle (NA201SX-4022; Olympus). Needle punctures were performed using the "jubbing" method (Figures 1, 2, 3).[14] Integrated color power Doppler ultrasound was used to avoid intervening vessels immediately before needle puncture.

It is recommended to use different needles for the biopsy of different nodal stationsin order to avoid contamination. However, we decided to use

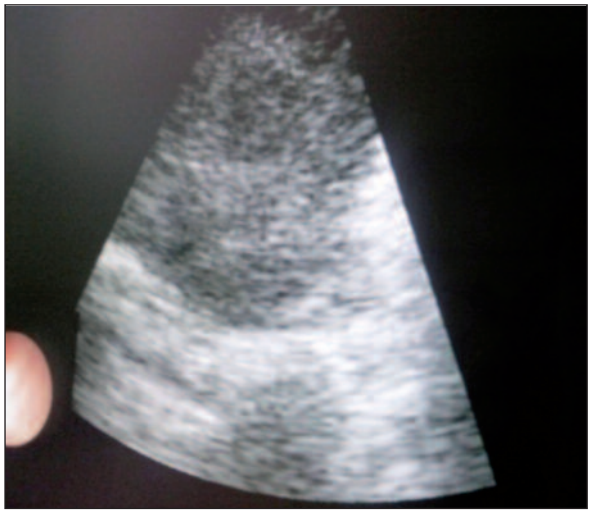

FIGURE 1: Ultrasonographic view of a lymph node located at 4R position.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

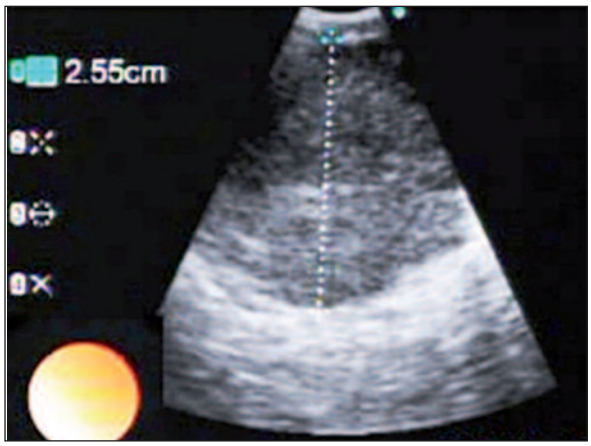

FIGURE 2: Measuring the diameter of a lymph node.
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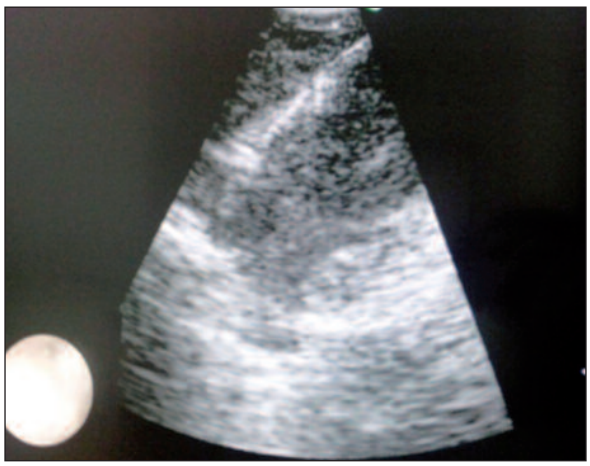

FIGURE 3: Needle aspiration of a lymph node.
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a single needle since since using different needles would increase the expenditures; therefore we sampled the lymph nodes in an prearranged manner. N3 nodes were sampled first, and then N2, and at last N1 nodes were punctured.

The aspirated material was smeared onto glass slides. Smears were air dried and stained using May Grünwald's eosin methylen blue (Merck KGaA, Germany) solutions. The solid substances in the aspiration needle obtained by EBUS-TBNA were put into 10% neutral buffered formalin. The remnants of aspirate were collected in a bottle filled with CytoRich Red Collection Fluid (Shandon, Thermo Scientific, England) for cell block. Tissue cores and cell blocks were stained with hematoxylin and eosin. Immunohistochemical evaluation was performed when necessary. A pathologist, blinded to the details of the patients, evaluated all the materials. Adequate cell material was defined as a specific diagnosis or the presence of lymphocytes on the specimen.

Mediastinoscopy was planned for the patients whose definite diagnosis was not established by EBUS-TBNA. Patients who refused the mediastinoscopy were followed up clinically with PET.

STATISTICAL ANALYSIS

Statistical analysis was done using the SPSS program (version 10.0). The diagnostic consistency was analyzed using the McNemar test. Descriptive values were given as median (min-max). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy rate for prediction of lymph node staging were calculated using the standard definitions.

RESULTS

The study was performed with 52 patients who underwent EBUS-TBNA; 46 men and six women (mean age 59.5 years, range 30-78 years). In these patients, 97 enlarged lymph nodes were identified by CT scanning which were bigger than 1 cm. Of these 97 nodes, 94 were successfully biopsied and a specific diagnosis was established (Table 1).

Of 97 lymph node biopsies, 70 lymph nodes were from mediastinal region and 27 were from

TABLE 1: Characteristics, diagnosis and location of target lesion in patients enrolled in the study.

	Data
Patients, No	52
Men/women	46/6
Diagnosis, No (Percent)	
Adenocarcinoma	10 (19.2%)
Large cell carcinoma	1 (1.9%)
Squamous cell carcinoma	11 (21.2%)
Nonsmall Cell Lung Cancer	17 (32.7%)
Small Cell Lung Cancer	13 (25%)
Lymph nodes, No	97

hilar region. 4R and 7 stations were the mostly sampled lymph node stations. The median short axis diameter of all sampled lymph node stations were between 1.58- 2.70 cm (Table 2). All of the 13 patients with small cell lung cancer (SCLC) and 36 out of 39 patients with nonsmall cell lung cancer (NSCLC) were diagnosed definitely with EBUS-TBNA. Cytological examinations of three lymph node biopsies taken with EBUS from three patients diagnosed as lung cancer were negative for malignancy. Two of these three patients gave their informed consents for mediastinoscopy. After mediastinoscopy, one lymph node was reported as malignant (false negative) and the other one was negative for malignancy (true negative). Other patient who did not give consent for mediastinoscopy was examined with PET. PET reported no involvement in mediastinal and/or hilar lymph nodes. This patient showed no evidence of clinical or radiological malignancy during follow up period (six months), therefore was accepted to have a benign disease (true negative) (Figure 4). When our data were analyzed with non-parametric McNemar test, no statistically significant result was found (p= 1.000) (Table 3). The sensitivity, specificity, PPV, NPV and diagnostic accuracy of EBUS-TBNA in the diagnostic evaluation of mediastinal and/or hilar lymph nodes of patients suspected for lung cancer were 98.9%, 100%, 100%, 67% and 98.9% respectively.

The definitive diagnosis of three lymph nodes was benign (two lymph nodes reactive and one lymph node tuberculosis) and 93 lymph nodes was malignant according to EBUS-TBNA (Table 4). Of 52 patients, 12 (23%) (9 NSCLC, 3 SCLC) had malignant N3 lymph node involvement as diagnosed by EBUS-TBNA.

Definitive diagnosis was done by EBUS-TBNA in 23 patients (44%) with lung cancer suspicion in whom no endobronchial lesion was detected by conventional bronchoscopy.

All patients tolerated the procedure very well and no complications associated with EBUS-TBNA were observed.

DISCUSSION

Chest physicians often need to evaluate enlarged mediastinal/hilar lymph nodes.[4,15] Lymph nodes may be enlarged due to a variety of inflammatory,

TABLE 2: Results of real-time EBUS-TBNA in 52 patients with mediastinal and/or hilar lymph nodes by location.

Lymph node station	Nodes (n) (%)	Short-axis diameter cm median (min-max)	Diagnosis established from biopsy
2R	2 (2.1)*		2
4R	20 (20.6)	2.70 (1.0-4.0)	20
4L	8 (8.2)	2.07 (1.0-4.0)	8
7	40 (41.2)	2.25 (0.8-3.0)	40
10R	13 (13.4)	2.28 (1.5-3.5)	13
10L	6 (6.2)	1.58 (0.9-2.0)	6
11R	5 (5.2)	2.00 (1.5-2.5)	5
11L	3 (3.1)**		2

* Short-axis diameters of two lymph node localized at 2R station were 2 cm and 3 cm.

** Short-axis diameters of three lymph node localized at 11L station were 1 cm, 2.5 cm and 3 cm.

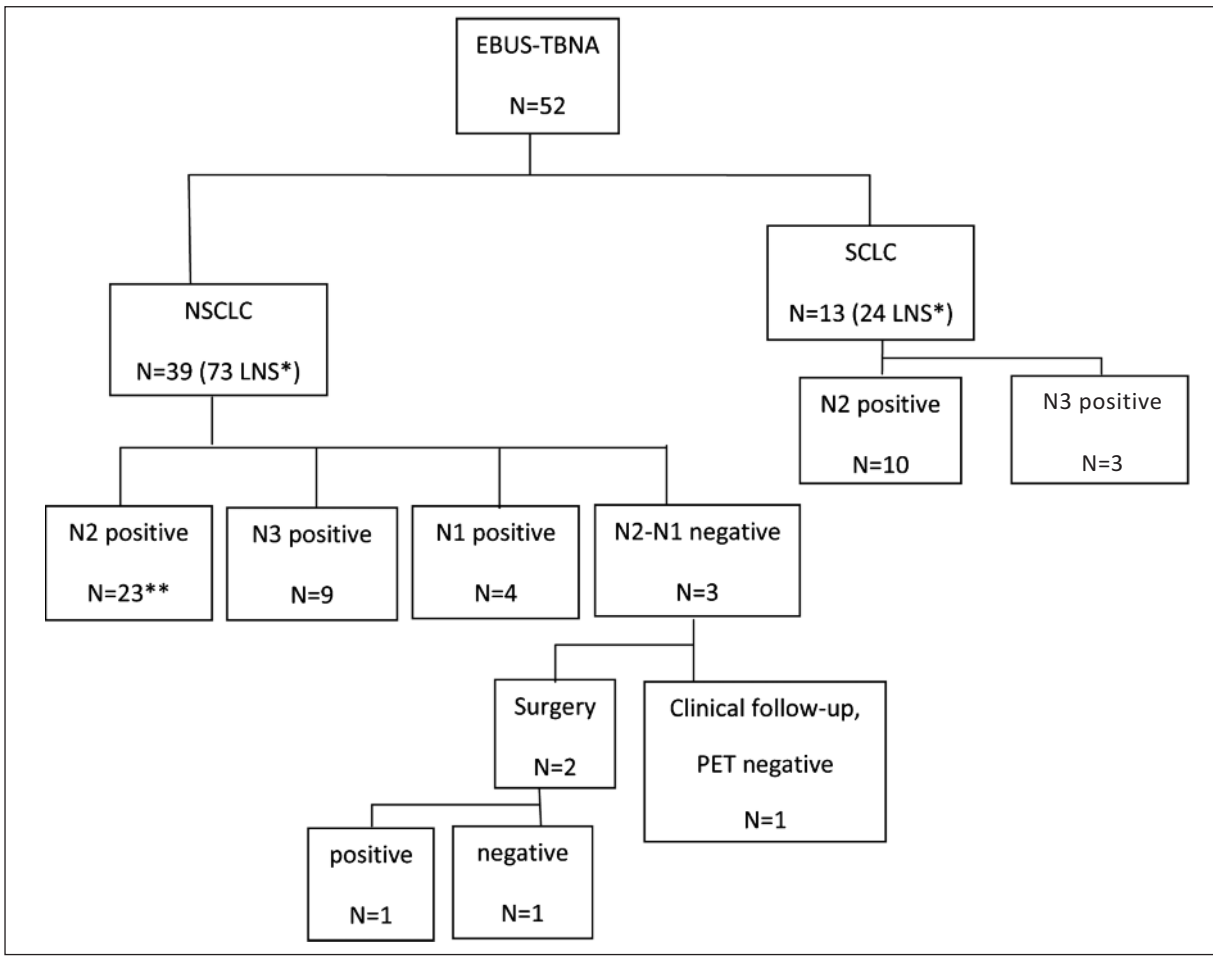

FIGURE 4: The clinical course of 52 patients who were enrolled in this study.
*Mediastinal LN stations, **22 malignant, 1 tuberculosis, NSCLC=Nonsmall Cell Lung Cancer, SCLC=Small Cell Lung Cancer).

TABLE 3: The diagnostic consistency of results obtained by McNemar test.

EBUS-TBNA	Mediastinoscopy / Clinical-radiological follow-up Specific diagnosis		
	Present	Absent	Total
Specific diagnosis			
present	94		94
absent	1	2	3
Total	95	2	97

p=1.000

infectious or malignant disorders, and it is important to ascertain a diagnosis, or in the case of malignancy, to determine the stage of the disease before deciding the treatment.[15]

Mediastinoscopy is considered as the "gold standard" for the evaluation of mediastinal lymph nodes. However, as a surgical procedure, it is costly, requires general anesthesia, and has associated morbidity and mortality.[16-18] The procedurehas some limitations since lymph nodes in the posterior carina and hilar stations are generally inaccessible. Furthermore, although it is currently the gold standard, the specificity and sensitivity of mediastinoscopy are not optimal.[19]

TABLE 4: Definitive diagnosis of lymph nodes.

Histopathological type	Lymph nodes (n)	Definitive diagnosis by EBUS n (%)	
		Benign	Malignant
Adenocarcinoma	24*	3 (15.8%)	23 (95.8 %)
Squamous cell carcinoma	19		16 (84.2%)
Large cell carcinoma	3		3 (100%)
NSCLC	27		27 (100%)
SCLC	24		24 (100%)

*A lymph node biopsy taken by EBUS-TBNA reported as malignancy negative and definitive diagnosis was made by mediastinoscopy.
NSCLC= Nonsmall cell lung cancer; SCLC= Small cell lung cancer.

Endoscopic imaging with simultaneous ultrasound scanning has several advantages over mediastinoscopy; there is no need for surgery or general anesthesia; it can be performed repetitively in the same person; and depending on which endoscopic modality is used, lymph node stations that are not surgically accessible can be reached.[20,21]

Indications for EBUS-TBNA are lymph node staging in lung cancer, diagnosis of intrapulmonary tumors, diagnosis of unknown hilar and/or mediastinal lymphadenopathies,and diagnosis of mediastinal tumors.[22] Yasufuku et al. investigated 70 patients with suspected lung cancer and enlarged mediastinal (n= 58), hilar (n= 12) lymph nodes with EBUS-TBNA.[11] The sensitivity, specificity and accuracy of EBUS-TBNA in distinguishing benign from malignant lymph nodes were 96%, 100% and 97%, respectively.[11] In a subsequent study from the same group on 108 consecutive patients with suspected lung cancer and enlarged mediastinal nodes on CT, EBUS-TBNA had a sensitivity of 94.6%, NPV of 89.5% and accuracy of 96% in assessing mediastinal nodes.[23] Herth et al. performed EBUS-TBNA in 502 patients with suspected lung cancer and enlarged mediastinal nodes on chest CT.[8] A total of 572 lymph nodes were punctured and 535 (94%) resulted in a diagnosis. In this study, a sensitivity of 94%, and specificity of 100% for mediastinal staging was reported.[8] Ernst et al. evaluated 213 patients with suspected NSCLC, and the patients with CT or PET-positive hilar lymph nodes underwent EBUS-TBNA.[24] Overall, diagnostic sensitivity of EBUS-TBNA was 91%, specificity was 100%, and positive predictive value was 92.4%.[24] Herth et al. studied the performance of EBUS-TBNA in the staging of patients with suspected tumors of pulmonary origin as evidenced by CT, but without enlargement of lymph nodes (nodes measuring <1 cm).[25] This study, which included 100 consecutive patients, sensitivity and NPV were reported as 92.3% and 96.3%, respectively. In another study, Herth et al.[26] determined the results of EBUS-TBNA in sampling mediastinal lymph nodes in 100 patients with NSCLC, who has radiologically normal mediastinum and no PET activity. Comparing all results with those based on surgical staging, the sensitivity for detecting malignancy was 89% and NPV was 98.9%.[26] Yasufuku et al. compared the efficacy of EBUS-TBNA against that of CT and FDG-PET.[27] This study included 102 patients with suspected or anatomopathologically confirmed lung cancer who were considered candidates for curative surgery. The sensitivity and NPV of EBUS-TBNA for predicting the stage of mediastinal lymph nodes were 92.3% and 97.4%, respectively. Using CT, these same parameters were 76.9% and 87.5% respectively; FDG-PET produced values of 80%, and 91.5% respectively. The specificity and sensitivity of EBUS-TBNA in staging of mediastinal lymph nodes of lung cancer patients were found as 100% (95% CI 96-100%), 100% (95% CI 91-94%) and 88% (95% CI 79-94%), 93% (95% CI 91-94%) respectively in two meta analyses.[28,29] In our study, no statistical difference was observed when other diagnostic procedures (mediastinoscopy or clinical follow-up) were compared to EBUS-TBNA for the definite diagnosis of our patient group. This result confirms the efficiency of EBUS-TBNA as a diagnostic tool. The sensitivity, specificity, PPV, NPV

and diagnostic accuracy of EBUS-TBNA in the evaluation of mediastinal lymph nodes of patients suspected for lung cancer were 98.9%, 100%, 100%, 67% and 98.9%, respectively. The ratios of sensitivity, specificity, PPV and diagnostic accuracy determined in our study are similar to those in the literature. However, NPV in our study is slightly lower than previous studies.[23,25,27] The low NPV in our study is possibly due to the experience of our team, the localization of lymph nodes and especially small metastases inaccessible with EBUS-TBNA. Tournoy et al. suggested that negative EBUS-TBNA results should be confirmed by other diagnostic methods.[30] In accordance with this point of view, one of our lung cancer patients with nonmalignant mediastinal lymph nodes which biopsy was taken with EBUS-TBNA was accepted as malignant after mediastinoscopy.

Twelve patients who had malignant N3 lymph node involvement diagnosed by EBUS-TBNA were avoided from invasive diagnostic procedures and taken to chemo-radiotherapy program immediately. Interestingly, 23 patients with lung cancer suspicion but no endobronchial lesions were diagnosed definitively as lung cancer by EBUS-TBNA without any requirement for further diagnostic procedures. The results in the literature also support this finding.[30-32]

EBUS-TBNA is accepted as a quite reliable diagnostic procedure without serious complications.[7,10,12,32] Rarely, cough, bleeding in the application point of needle and clinically unimportant infections were reported as complications.[33,34] No complications were observed in our study.

This study has some limitations. Our team is new in applying EBUS-TBNA and will gain experience. The results are affected the most from clinical experience. The other limitation is the use of CT in all patients but PET in only a small proportion of them.

In conclusion, EBUS-TBNA is an effective and reliable diagnostic procedure in the evaluation of mediastinal and/or hilar lymph nodes of patients suspected for lung cancer. Moreover, it is a very useful diagnostic tool in the presence of mediastinal and/or hilar lymph nodes which are unreachable to by conventional bronchoscopy.

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