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Original Article

The impact of EBUS-TBNA, F-18 FDG PET SUV-max value, and tomographic measurement of lymph node density in the diagnosis of mediastinal malignant lymph nodes

Necati Solak [1]*, Mehmet Cetin [1], Mehmet Buyukevli [1], Busra Ozdemir Ciftlik [2], Koray Aydogdu [1], Serdar Han [1], Tevfik Kaplan [1]

[1]Health Sciences University, Ankara Etlik City Hospital, Thoracic Surgery Clinic, Ankara, Türkiye
[2]Kirikkale University School of Medicine, Department of Thoracic Surgery Ankara, Türkiye

ABSTRACT

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive effective, simple procedure and has replaced mediastinoscopy in diagnosis of mediastinal lymphadenopathies. But still there is an effort to increase diagnostic value of EBUS-TBNA and to meet additional information to guide biopsy especially in false negative situations.

Materials and Methods: In this retrospective study between December 2022 and December 2023, 90 patients, 176 lymph nodes were sampled with EBUS-TBNA. Patients' characteristics, lymph node density on CT, PET-CT findings, pathological diagnosis by EBUS-TBNA, and surgery were all written down.

Results: Sensitivity, specificity, negative predictive value, and positive predictive value of EBUS-TBNA were 78.8%, 95.8%, 85%, and 90.3%, respectively. Mean SUV-max values in PET tomography were 2.66±0.56 in benign lymph nodes, whereas it was 9.26±2.34 in malignant lymph nodes and this was significantly higher than benign lymph nodes (p<0,001). For detecting malignancy, cut-off value of SUV-max was found 6.02±1.84 and sensitivity and specificity were 55.3%, 95.8% respectively (AUC= 0,895 95% CI (0,844-0,946), p<0.001). Mean tomographic lymph node density was 25.05±4.67 HU in benign lymph nodes. Also mean tomographic lymph node density was 31.55±5.34 HU and significantly higher than benign lymph nodes (p=0.03). Cut-off value of density for detecting malignancy was found 29,05±4.78 and sensitivity and specificity were 65.0%, 56.2% respectively (AUC= 0,585 95% CI (0,500-0,670), p=0.05).

Conclusions: EBUS has a key role in differential diagnosis of lymphadenopathies. PET tomography SUV-max value and tomographic lymph node density could help clinician to increase diagnostic value of EBUS in borderline suspicious lymphadenopathies.

Keywords: density, SUV-max, EBUS-TBNA, mediastinal lymph node

Corresponding Author*: Necati Solak, MD. Ankara Etlik City Hospital, Thoracic Surgery Clinic, Varlık Mahallesi, Halil Sezai Erkut Caddesi, 06170, Yenimahalle, Ankara, Türkiye.
E-mail: n.solak80@gmail.com Phone: +90 5064727747
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Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive procedure used in the diagnosis of mediastinal lymphadenopathies and masses. It is frequently used in the preoperative staging of lung cancer cases, especially in thoracic surgery clinical practice [1]. The absence of metastatic N2 and N3 lymph nodes in the mediastinal area is one of the operability criteria in lung cancer cases. In malignancies with mediastinal lymphadenopathies, the samples of lymph nodes are required to be obtained before deciding the treatment.

In a patient with lung cancer, central tumors, mediastinal lymph nodes larger than 1 cm on computed tomography (CT), significant standardized uptake value (SUV) on positron emission tomography (PET), diagnosis of adenocarcinoma, and tumors larger than 3 cm are indications for mediastinal sampling [2]. The gold standard for mediastinal lymph node sampling is mediastinoscopy. However, in recent years, EBUS-TBNA has been preferred over mediastinoscopy because it is less invasive, simple, effective and has a low morbidity and mortality, can directly visualize the lesion and adjacent structures, can be repeated, and has a high diagnostic value [1,3]. However, mediastinoscopy may be required, if the results are negative in EBUS-TBNA. All efforts should be done to increase the diagnostic value of EBUS-TBNA and provide additional information to guide the biopsy in performing the procedure.

In this study, we aimed to investigate the diagnostic value of EBUS-TBNA, the computed tomographic density and SUV-max value of lymph nodes for the diagnosis of mediastinal lymph nodes in pulmonary and extrapulmonary malignancies.

Materials and Methods

This retrospective analysis included patients with hilar and/or mediastinal lymphadenopathy who underwent EBUS-TBNA of lymph nodes in our thoracic surgery department between December 2022 and December 2023. In our clinic, EBUS-TBNA is performed for staging in patients with pulmonary and extrapulmonary malignancies with hilar and/or mediastinal lymphadenopathies and for diagnostic purposes in patients without a diagnosis of malignancy. The exclusion criteria comprised patients with incomplete clinical data, those lacking definitive pathological diagnosis or adequate follow-up information, and patients who underwent EBUS-TBNA following induction therapy. We obtained local ethics committee approval from Health Sciences University, Ankara Etlik City Hospital (AEH-BADEK-2024-134) before the study and conducted it in accordance with the Helsinki Declaration of Human Rights.

The patients' age, gender, the type of malignancy, the density of lymph nodes on CT (average Hounsfield Unit (HU)), SUV-max of lymph nodes on 18F-FDG PET/CT, reports of EBUS, aspirated LN stations, any complications, the histopathological diagnosis by EBUS-TBNA, and surgery were all recorded.

All EBUS-TBNA procedures were performed by experienced thoracic surgeons. All lymph nodes with a PET SUV-max value ≥ 2.5 and/or a size greater than 5 mm as determined by EBUS were sampled (Figure 1). The EBUS-TBNA procedure was performed under general anesthesia using a laryngeal mask airway (LMA). The procedure was carried out with a convex-probe EBUS bronchoscope, and a single 22G EBUS needle was used for each patient.Lymph node sampling was initiated in accordance with standard staging principles, following the sequence N3 ± N2 ± N1. At least four needle passes were performed from each lymph node station. Rapid on-site cytological evaluation (ROSE) was applied.

Patients who did not undergo surgical intervention were followed for a minimum duration of six months. The diagnostic accuracy of lymph nodes classified as benign by EBUS was assessed based on interval changes in lymph node size observed on computed tomography performed at least six months later [4].

Sensitivity, specificity, negative and positive predictive value, were calculated based on CT or PET-CT images at least 6 months later, the final diagnosis of mediastinal and hilar LNs, and surgical pathology.

Statistical Analysis

The SPSS 24.0 package evaluated all analyses in the study. Descriptive statistics were presented as number of units (n), percentage (%), mean ± standard deviation (mean ± SD) for age. Patients were divided into groups

according to malignant/benign pathology and pulmonary/extrapulmonary malignancy on EBUS-TBNA. The student's t-test was used for numerical variables that fell within the normal distribution range between paired groups, and the Mann-Whitney U test was used for continuous numerical variables without normal distribution. Sensitivity and specificity values, as well as the cut-off value of SUV-max measured by PET-CT, were evaluated by ROC analysis. We used Pearson chi-squared analysis to compare the distribution of categorical variables between groups. A p-values below 0.05 were considered statistically significant.

Results

The study included 90 patients who underwent EBUS-TBNA in our clinic. Age, sex, primary diagnosis, number of lymph nodes sampled per patient, median lymph node size, mean lymph node SUV-max value, mean lymph node density (HU), and post-procedure pathology result (malignant, benign, non-diagnostic) are shown in Table 1. PET tomography findings taken at an external center could not be obtained in 15 patients (15.9%). In 9 patients EBUS procedure were non-diagnostic. No complications were observed during or after EBUS-TBNA.

A total of 176 LNs were sampled in 90 patients. The mean number of LNs sampled was 1.96±0.75, and in 23 (25.6%) patients TBNA was performed from a single lymph node. The numbers and proportions of lymph node areas sampled are shown in Figure 2.

In 25 patients who underwent surgery we were able to make a confirmation of EBUS-TBNA lymph nodes histopathology with surgical histopathology. Only in 3 (12%) patients and only in one mediastinal lymph node station malignancy was detected in surgical histopathology whereas EBUS-TBNA histology were negative for malignancy in these patients.

Sensitivity, specificity, negative predictive value, and positive predictive value of EBUS-TBNA were 78.8%, 95.8%, 85%, and 90.3%, respectively.

The comparison results of malignant and benign lymph nodes after EBUS-TBNA in terms of density, size, and SUV-max values are shown in Table 2.

The mean size of benign lymph nodes was 13 ± 2.56 mm whereas it was 21±3.78 mm in malignant lymph nodes and this was significantly higher than benign lymph nodes (p<0.001).

Mean SUV-max values in PET tomography were 2.66±0.56 in benign lymph nodes, whereas it was 9.26±2.34 in malignant lymph nodes and this was significantly higher than benign lymph nodes (p<0,001). For detecting malignancy, cut-off value of SUV-max was found 6.02±1.84 and sensitivity and specificity were 55.3%, 95.8% respectively (AUC= 0,895 95% CI (0.844-0.946), p<0.001) (Figure 3).

Mean tomographic lymph node density was 25.05±4.67 HU in benign lymph nodes. Also mean tomographic lymph node density in malign lymph nodes was 31.55±5.34 HU and this was significantly higher than benign lymph nodes (p=0.03). Cut-off value of density for detecting malignancy was found 29.05 ±4.78 and sensitivity and specificity were 65.0%, 56.2% respectively (AUC= 0.585 95% CI (0.500-0.670), p=0.05) (Figure 4).

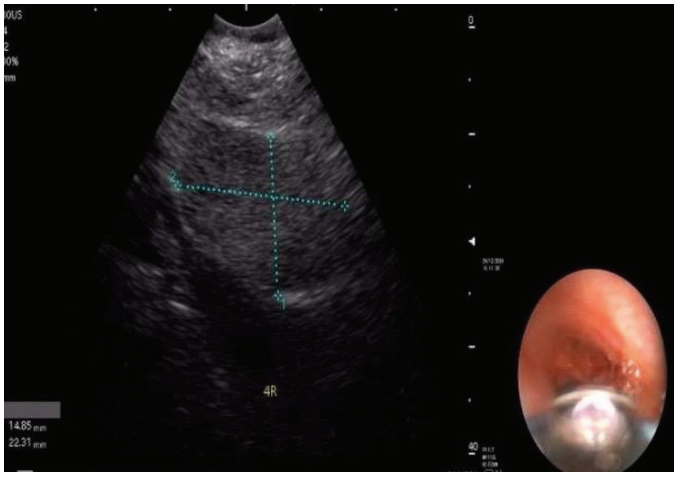

Figure 1. Endobronchial ultrasound image.

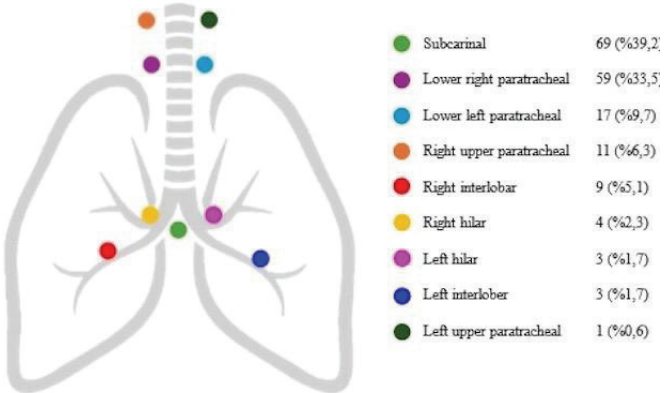

Figure 2. Number and percentage of lymph nodes sampled in EBUS-TBNA.

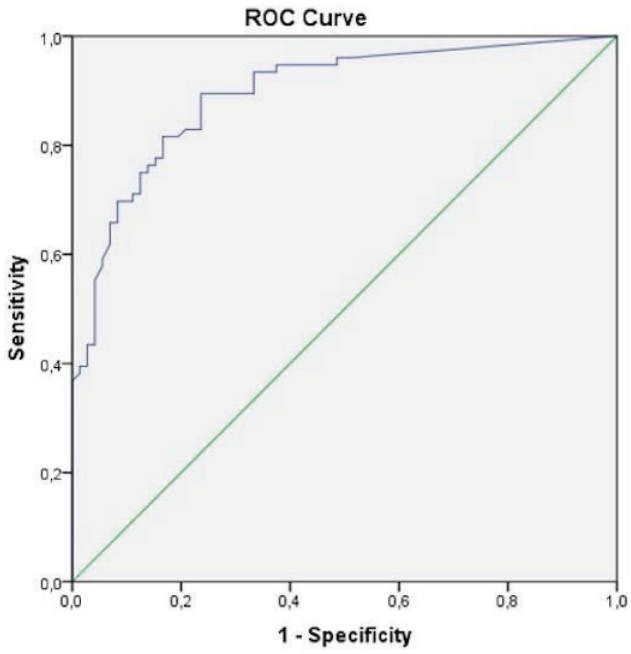

Figure 3. Lymph node PET CT SUV-max value ROC Curve.

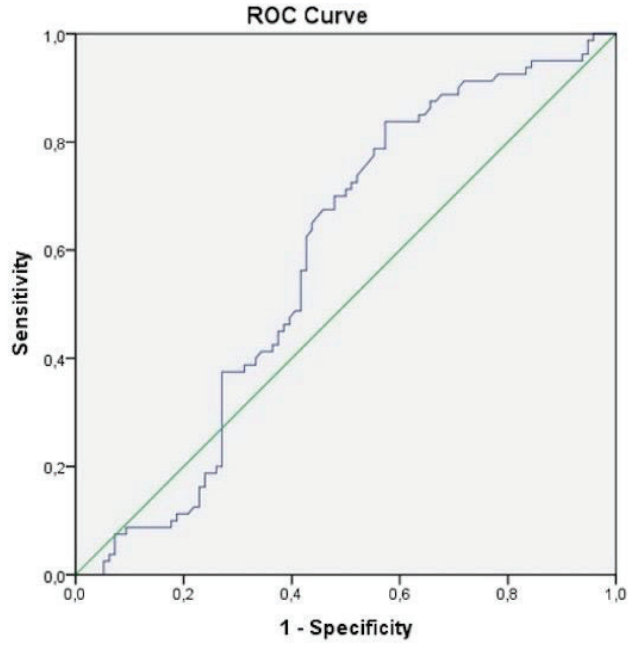

Figure 4. Lymph Node Tomographic density ROC Curve.

Discussion

Mediastinoscopy is the gold standard for mediastinal lymph node biopsy, but EBUS-TBNA has recently been defined as the preferred method due to its high diagnostic value and repeatability with lower morbidity and mortality [1, 3]. Yasufuku et al. found the sensitivity, specificity, and negative predictive value of EBUS-TBNA to be 94.6%, 100%, and 89.5%, respectively [5], while a meta-analysis study reported sensitivity of 52-92%, negative predictive value of 57-93%, and accuracy of 84-96% [6]. In our study, the sensitivity, negative predictive value, and diagnostic accuracy of EBUS-TBNA were found to be 78.8%, 85%, and 90.3%, respectively, and they were generally compatible with the literature.

The imaging diagnosis of malignant mediastinal lymph node mainly defines to the parameters of lymph node morphology, metabolism on PET-CT, size, and density, which mainly depends on the clinical experience of the physician [7]. The features of the lymph nodes influence target selection during EBUS-TBNA. In this study we evaluate the features of the lymph nodes to guide biopsy and to increase diagnostic value of EBUS-TBNA.

PET-CT is considered a non-invasive and effective imaging modality for determining malignant mediastinal lymph nodes, but especially false negative and positive situations are still significant problems. In our study sensitivity and specificity of PET-CT were 55.3%, 95.8% respectively which are similar to the results of previous studies [8, 9]. In our study, the SUV-max value of malignant lymph nodes was significantly higher than that of benign lymph nodes. There are studies showing that PET-CT is superior to other imaging modalities for mediastinal staging and detection of distant metastases in patients with malignancies. The SUV-max value of malignant lymph nodes was found to be significantly higher than that of benign lesions, but no difference was found according to histological subtype [10]. A high SUV-max uptake on PET CT shows high specificity but moderate sensitivity, so additional criteria are needed for target selection to increase the diagnostic value of EBUS-TBNA.

In lymph node density measurements, the cut-off value for benign-malignant differentiation was found to be 30 HU, and both density and SUV-max values for malignant lymph nodes were significantly higher than benign lymph nodes. Flechsig et al. reported that in a study of 248 lymph nodes in 122 patients, the density of malignant lymph nodes was significantly higher than that of benign lymph nodes, but no significant difference was found between histological subtypes of malignant lymph nodes. In the same study, the cut-off value for lymph node density was found to be 20 HU [10]. In another study, the cut-off value for lymph node/aorta density ratio was found to be 0.9, and it was reported to be

significant above 0.9 in malignant lymph nodes [11]. A higher density in lymph nodes thought to be associated with malignancy due to loss of the fatty hilar structure that is generally used as an index of benign situations of lymph node. In our study, we think that the higher rate of regional infections and granulomatous disease may be effective in the higher cut-off value of lymph node density in malignant-benign differentiation.

In a meta-analysis by de Langen et al. lymph nodes measuring 16 mm or bigger on CT found to have a malignant probability of 20% [12]. In another study by Ikeda K et al. the short and the long axis diameter of metastatic lymph nodes were found to be bigger than non-metastatic lymph nodes in lung cancer [13]. In this study we found the size of lymph nodes were bigger in malignant lymph nodes and this was statistically significant.

Zhang et al. described complications in 4 patients after EBUS-TBNA in their evaluation of 248 patients. They reported severe cough in 2 of these patients and low saturation during the procedure in 2 patients [14]. In another study, EBUS-TBNA was performed in 161 patients, and no complications were reported [15]. We observed no complications in any of the patients in our study. One of the reasons for the general preference for EBUS-TBNA is that it leads to a low morbidity-mortality rate with a low complication rate.

Limitations of the Study

The principal limitations of our study include its retrospective design and relatively small sample size, the lack of confirmatory mediastinoscopy in patients who underwent EBUS-TBNA, and the unavailability of data from certain examinations performed at external centers.

The main value of our study is that the team performing EBUS-TBNA also performed lymph node dissection in the same patient. We believe that this situation enhances the accuracy of the results. In addition, an evaluation of lymph node density with different variables will contribute to the literature in terms of indications for sampling mediastinal lymph nodes.

In conclusion, EBUS-TBNA is a method of mediastinal lymph node sampling that can be safely used in the clinics. Computed tomographic density, size and SUV-max value of lymph nodes could help physician for guiding biopsy especially in false negative situations. Larger prospective studies are needed to investigate these parameters especially in false-negative results.

Declaration of conflicting interests

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Ethics approval

This study was approved by local ethics committee of Health Sciences University, Ankara Etlik City Hospital (AEH-BADEK-2024-134).

Authors' contribution

N.S.: Conceptualization, methodology, data curation, writing - original draft, project administration. M.Ç.: Investigation, resources, validation, writing - review & editing. M.B.: Data curation, formal analysis, visualization. B.Ö.Ç.: Investigation, resources, writing - review & editing. K.A.: Supervision, validation, writing - review & editing. S.H.: Supervision, validation, writing - review & editing. T.K.: Conceptualization, supervision, validation, writing - review & editing.

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