Medicine®

OPEN

Evaluation of hypermetabolic mediastinal-hilar lymph nodes determined by PET/CT with EBUS-TBNA and calculation of SUVmax cutoff values in differentiation of malignancy

Erhan Ugurlu, MD[a], Melis Metin, MD[a], Nazli Cetin, MD[a],* iD, Emel Kilicarslan, MD[b], Serkan Degirmencioglu, MD[c], Tarik Sengoz, MD[d], Ilknur Hatice Akbudak, MD[e], Gamze Gokoz Dogu, MD[c], Umit Aydogmus, MD[f]

Abstract

Computed tomography (CT) and positron emission tomography (PET) are the most commonly used methods for diagnosis and staging in both malignant and benign diseases of the lung parenchyma and mediastinum. Endobronchial ultrasonography (EBUS) guided transbronchial needle aspiration biopsy (TBNA) has become widespread in recent years because it allows minimally invasive tissue sampling. PET-CT has high sensitivity in the diagnosis of malignancy but has low specificity. The false positive rate is high with the SUVmax 2.5 cutoff value, which is widely used in studies about malignancy. In our study, we evaluated lymph nodes with high F18-fluorodeoxyglucose (FDG) uptake on PET/CT and sampled by EBUS-TBNA. We aimed to calculate the new SUVmax cutoff values in the differentiation of malignancy. Our study included 103 patients who were examined for any reason and who underwent biopsy with EBUS-TBNA due to mediastinal or hilar lymph node enlargement on PET-CT. The relationship between PET-CT findings and EBUS findings, EBUS-TBNA results was evaluated. Biopsies were taken from 140 lymph nodes in 103 patients included in our study, and 39 (27.8%) were diagnosed as malignant. In our study, when the SUVmax cutoff value in PET-CT is taken as 2.54, the sensitivity is 98%, but the specificity remains at the level of 12%. When the SUVmax cutoff value in PET-CT was taken as 4.58, the sensitivity was 92% and the specificity was 49%. When this value was accepted as 5.25, and 6.09 the sensitivity was respectively 90% and 85%, the specificity was respectively 52% and 60%. In evaluations, we conducted in order to determine different SUVmax cutoff values that can be used for higher sensitivity and specificity in malignancy studies, the cutoff values were 4.58, 5.25, and 6.09. It is thought that these cutoff values will be useful both for diagnosing malignancy and for distinguishing benign pathologies.

Abbreviations: CT = computed tomography, EBUS = endobronchial ultrasonography, FDG = F18-fluorodeoxyglucose, PET = positron emission tomography, SUVmax = maximum standardized uptake value, TBNA = transbronchial needle aspiration biopsy.

Keywords: EBUS, PET-CT, sensitivity, specificity, SUVmax

1. Introduction

Early and accurate diagnosis is very important for the treatment of lesions in the lung parenchyma and diseases involving lymph nodes in the mediastinum. Malignant diseases such as primary lung cancer, metastases, lymphomas and various benign diseases such as sarcoidosis, tuberculosis and infections may present with involvement in both the lung parenchyma, mediastinal and hilar lymph nodes. Cancer staging is the basis of the choice of lung cancer treatment scheme.[1–4]

The mostly used methods for diagnosis and staging are computed tomography (CT) and positron emission tomography (PET), which are noninvasive imaging methods.[1,3,5] The addition of histopathological evaluation to these imaging methods increases the diagnostic accuracy.[1,2,6] Surgery is the gold standard method in staging by histopathological evaluation.[1] The use of minimally invasive methods in staging reduces the need for surgical intervention.[1,6] Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) stands out as it is a minimally invasive method. The low risk of major complications also allows it to be used safely.[1,4] Increasing the diagnostic accuracy of EBUS will help reduce major surgical interventions. Increasing the predictive properties of the parameters used in CT and PET methods used as a guide before EBUS-TBNA will increase the accuracy of EBUS. PET-CT has high sensitivity in the diagnosis of malignancy. However, the specificity is lower.[1,6,7] The reason for this is that benign pulmonary, mediastinal, hilar lesions and inflammatory processes that cause high metabolic activity can cause false positives in PET.[7,8] PET positivity is determined based on the maximum standardized uptake value (SUVmax) of F18-fluorodeoxyglucose (FDG). The malignancy rate is high in lymph nodes with large size and high FDG uptake in PET-CT. The SUVmax cutoff value which is commonly used to detect malignancy, is 2.5. When the SUVmax cutoff value is accepted as 2.5, false positivity is at a rate that should be taken into account.[9]

Since the false positivity is high with the SUVmax value of 2.5 which is used as cutoff in malignancy studies in PET-CT, investigations are carried out for using different cutoff values. Recent studies have suggested findings showing that the acceptance of SUVmax as 4, 4.31, and 5.2 increases the sensitivity and specificity in the diagnosis of malignancy.[3,7,10] However, a clear cutoff that can be used in malignancy studies regarding SUVmax value has not been determined yet. In this study, we aimed to calculate the malignant/benign ratio of biopsies taken by EBUS-TBNA from mediastinal and hilar lymph nodes with high FDG uptake in PET/CT and to calculate the SUVmax cutoff value in malignant cases.

2. Methods

2.1. Patient selection

All patients (n = 103) who had enlarged mediastinal or hilar lymph nodes on PET-CT (SUVmax value of 2.5 and above), giving informed consent, no contraindication to receive general anesthesia/deep sedation and underwent EBUS-TBNA between March 2019 and June 2020 were included in the study. Patients who do not accept the procedure or are not at the level of consciousness to give consent, are not suitable for anesthesia, have uncontrolled coagulopathy or bleeding diathesis, have uncontrolled heart failure, have uncontrollable angina or severe arrhythmia, and have had myocardial infarction or cerebrovascular accident in the last 6 months were excluded from the study.

Demographic data of the patients, evaluations made before the procedure, imaging findings, characteristics of the lesion that was taken biopsy during the EBUS procedure and ultrasound images were recorded prospectively.

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of our university with the decision dated 05.03.2019 and numbered 05. Before the procedure, "Information and Consent Form" giving detailed information about the interventional procedure and their acceptance of the procedure and "Voluntary Consent Form" indicating that they agreed to use the data in the study were obtained from all patients.

2.2. EBUS procedure

Patients whose PET-CT imaging was performed and EBUS was planned were informed before the procedure and their consent was obtained, bleeding drugs and food intake were stopped 6 hours before the procedure. Preoperative evaluation was made in terms of suitability for anesthesia. For this purpose, complete blood count, biochemistry and coagulation values were measured; chest x-ray and electrocardiogram were taken.

In our study, Funion Fujifilm EB-530US Convex Ultrasound Bronchoscope EBUS device and SU-1 Ultrasound Processor device were used. The COOK ECHO-HD-22-EBUS-O-C ultrasonic biopsy needle was chosen for the aspiration biopsy. A single-use aspiration biopsy set with a proximal aspiration mechanism and a 22-gauge needle in a flexible catheter was used for each patient.

Local anesthesia with lidocaine and premedication and deep sedation using metoclopramide, midazolam, propofol, fentanyl were applied to eligible patients under operating room conditions. A mouthpiece was placed in the mouth after sedation. With the bronchoscope of EBUS, the tracheobronchial system was entered through the glottic space and appropriate areas were detected with the bronchoscopic view. When it came to the area to be examined, the image was taken by leaning the ultrasound probe against the wall. If necessary, during the procedure, the balloon was filled with sterile saline and the ultrasonic image became clear. During the procedure, the lesion diameter was measured and its localization was recorded. Before the biopsy, the tip of the bronchoscope was straightened and the needle sheath was removed. The length of the needle was adjusted and the lesion was inserted through the intercartilage space. In the meantime, to make sure that the needle was inside the lesion, the stylet inside the needle was pushed forward inside the lesion and its location was determined and then removed. Then, an injector was placed behind the needle, applying negative pressure. Aspiration biopsy was taken with negative pressure applied while the needle was moved back and forward. Vascular structures and vascularization characteristics of the lesion were evaluated using the Doppler mode when necessary during the procedure.

Since the same needle will be used in cases where sampling will be made from more than 1 station in the same patient, attention was paid to the order of application. A separate evaluation was made for each patient according to the location of the lesions and sampling was performed in the order of N3, N2, and N1.

Samples taken by aspiration biopsy were placed in a solution (red solution) approved by the pathology unit. The tissue was fixed and the cell block was made and it was prepared for pathological evaluation. Some of the tissue samples taken in cases with a preliminary diagnosis of tuberculosis or for the differential diagnosis of granulomatous disease were sent to the microbiology laboratory in sterile saline for culture.

2.3. Statistical analysis

The data were analyzed with the SPSS 25.0 package program. Continuous variables are given as mean ± standard deviation, median (minimum-maximum values) and categorical variables are given as numbers and percentages. The convenience of the data to the normal distribution was examined with Kolmogorov–Smirnov and Shapiro–Wilk tests. When the parametric test assumptions were met, the significance test of the difference between the 2 means was used in the comparison of independent group differences; when parametric test assumptions were not met, Mann–Whitney U test and Kruskal–Wallis analysis of variance were used to compare independent group differences. Differences between categorical variables were analyzed by Chi-square analysis. ROC analysis method was used to examine the method performances. As a result of the ROC

analysis, Youden Index value was used to determine the most appropriate cutoff point. Youden Index is obtained by subtracting 1 value from the sum of the sensitivity and selectivity values. The highest Youden Index value shows the cutoff point with the highest predictive power. As a result of the examinations made with the most appropriate cutoff points obtained from Youden Index values, sensitivity and selectivity values were obtained and the performance results were examined. $P < .05$ was considered statistically significant.

3. Results

The majority (71.8% (n = 74)) of the patients in our study were male and 28.2% (n = 29) were female. Median age for female (min-max) 62 (38–89); male were 61 (32–80). The median age of all patients was 61 (32–89). Male had a mean smoking history of 39.5 ± 29.1 pack-years, while female had a smoking history of 1.1 ± 5.5 pack-years. All patients had a mean smoking history of 28.68 ± 30.3 pack-years and a median of 20 (0–120) pack-years.

Sampling was performed with EBUS-TBNA from 140 lymph node stations in 103 patients who participated in our study. The characteristics of all lymph nodes sampled with EBUS-TBNA are shown in Table 1.

Thirty-nine (27.8%) of 140 lymph node biopsies were evaluated as malignant and the remaining 101 lymph nodes (72.2%) were evaluated as benign. Seven lymph nodes (5%) were evaluated as granulomatous inflammation and 94 lymph nodes (67.2%) as malignant negative. The characteristics of those evaluated as malignant negative are shown in Table 2. Among the lymph nodes evaluated as negative for malignancy in EBUS-TBNA, 34 lymph nodes in a total of 20 patients were evaluated with advanced surgery. Seventeen of these patients underwent mediastinoscopy; lobectomy/resection/lymph node excision with video-assisted thoracic surgery was performed directly in 3 patients and after mediastinoscopy in 1 patient (Table 3). The results after further examination or follow-up of 94 lymph nodes that were evaluated as malignant negative in EBUS-TBNA are shown in Table 4.

The mean dimensions of lymph nodes measured on PET-CT were calculated as 21.95 ± 12.74 (6.7–90). The mean size of lymph nodes measured during the EBUS procedure was evaluated as 18.79 ± 6.70 (8–40). The mean size of 101 (72%) benign lymph nodes measured on PET-CT was calculated as 19.19 ± 8.89 mm (6.7–70). The mean size was calculated as 29.10 ± 17.69 mm (10.9–90) in 39 (28%) malignant lymph nodes. When the dimensions measured during the EBUS procedure were evaluated, the mean size in benign lymph nodes (72%, n = 101) was calculated as 17.34 ± 6.01 mm (8–33). The mean size was calculated as 22.55 ± 7.01 mm (11–40) in malignant lymph nodes (28%, n = 39).

When the relationship between lesion size and being malignant or benign was evaluated, it was found that both the dimensions of the malignant lymph nodes measured on PET-CT and the dimensions measured during the EBUS procedure were significantly higher than the benign lymph nodes. (respectively, $P = .0001$, $P = .0001$).

The mean SUVmax value of 101 (72%) lymph nodes with negative EBUS-TBNA results was calculated as 5.63 ± 3.57 (0–19). The mean SUVmax value of 39 (28%) lymph nodes evaluated as malignant by EBUS-TBNA was calculated as 7.87 ± 2.67 (1.9–14). Accordingly, SUVmax value measured in PET-CT was found to be higher in lymph nodes that were evaluated as malignant as a result of pathology, compared to benign ones. ($P = .0001$).

When we examined the relationship between the rates of malignant and benign results of EBUS-TBNA and the SUVmax value measured in PET-CT, important points to be considered were determined. The excitatory threshold value of SUVmax cutoff value in PET-CT is accepted as 2.50 in malignancy studies. In our study, when the SUVmax cutoff value in PET-CT is taken as 2.54, the sensitivity is 98% but the specificity remains at the level of 12%. Although this value is appropriate and highly accurate for recognizing the patient group, it is extremely insufficient to distinguish benign conditions. The relationship between sensitivity and specificity according to the SUVmax cutoff value measured in PET-CT is shown in Table 5.

4. Discussion

When the pathology results of 140 lymph nodes were evaluated from which biopsies were taken, 39 (28%) lymph nodes were diagnosed as malignant as a result of EBUS-TBNA. In these lymph nodes, 14 (10%) are small cell carcinoma, 13 (9.3%) are adenocarcinoma, 4 (2.9%) are squamous cell carcinoma, 2 (1.4%) are non-small cell carcinoma of the lung, 2 were breast carcinoma metastasis (1.4%) and one of them was carcinoma metastasis of pancreaticobiliary system origin. When compared in terms of the distribution of malignant results, our study shows a great deal of similarity with the studies in the literature.[7,11] Although adenocarcinoma is mostly located peripherally as a primary tumor, its prevalence is high among malignancies in the community.[12] The high incidence of adenocarcinoma diagnosis among malignancies in our study group is thought to be related to the prevalence of lung adenocarcinoma in the community. In addition, although adenocarcinoma is mostly a peripheral tumor, it can metastasize to mediastinal and hilar lymph nodes and tumors can be seen in more than 1 metastatic focus in the lung parenchyma. Therefore, the diagnosis can be made from lymph node metastasis or an accessible metastatic nodule.[12–14]

In our study, when the data of 94 lymph nodes were evaluated which were reported as negative as malignancy in the pathology result of the biopsy taken with EBUS-TBNA; 7 lymph nodes (7.5%) were found to be malignant after further examination with surgical biopsy and 21 lymph nodes (22.3%) were found to be malignant in the EBUS-TBNA/ percutaneous

---

Table 1

Characteristics of lymph nodes performed EBUS-TBNA.

Lymph node stations, n (%)	
2R	6 (4.3)
4R	35 (25)
4L	6 (4.3)
7	41 (29.3)
10R	22 (15.7)
10L	16 (11.4)
11R	8 (5.7)
11L	6 (4.3)
Total	140 (100)
Lymph node size (PET-CT measurement), mm (mean ± SD)	21.95 ± 12.74
Lymph node size (EBUS measurement), mm (mean ± SD)	18.79 ± 6.70
SUVmax value of lymph nodes in PET-CT (mean ± SD)	6.28 ± 3.45
Pathology results of lymph nodes, n (%)	
Small cell carcinoma	14 (10)
Adenocarcinoma	13 (9.2)
Squamous cell carcinoma	4 (2.9)
Non-small cell carcinoma (NOS)	2 (1.4)
Cytology with suspicious malignancies*	3 (2.1)
Other**	3 (2.1)
Malignant negative cytology	94 (67.1)
Granulomatous inflammation	7 (5)
Total	140 (100)

CT = computed tomography, EBUS = endobronchial ultrasonography, PET = positron emission tomography, SUVmax = maximum standardized uptake value.

*Squamous cell carcinoma by bronchoscopic biopsy, malignant epithelial tumor metastasis by mediastinoscopy, reactive lymph node by mediastinoscopy but lymphoma involvement by clinical follow-up.

**Breast carcinoma metastasis (2), pancreaticobiliary carcinoma metastasis.

Table 2

Further examination/follow-up/council evaluation status of malignant negative lesions in lymph nodes performed by EBUS-TBNA.

	Lymph nodes, n (%)
Undergone surgical biopsy	34 (36.2)
Concurrently diagnosed with malignancy by EBUS from another focus	5 (5.3)
Diagnosed by concurrent bronchoscopic biopsy or PTAB	6 (6.4)
Diagnosed as metastatic malignancy due to a diagnosis of malignancy in another focus	9 (9.6)
Surgical biopsy was recommended but could not performed	17 (18.1)
Thorax CT follow-up	16 (17)
Considered as tuberculosis	4 (4.2)
Considered as benign	3 (3.2)
Total	94 (100)

CT = computed tomography, EBUS = endobronchial ultrasonography, PTAB = percutaneous transthoracic aspiration biopsy.

Table 3

Distribution of pathology results in patients with further examination by surgical biopsy.

Pathology result	Lymph nodes, n (%)
Chronic granulomatous inflammation	19 (55.9)
Lymphoma*	6 (17.7)
Reactive lymph nodes	5 (14.7)
Lymph nodes with the signs of anthracosis	2 (5.9)
Malignant epithelial tumor metastasis	1 (2.9)
Non-diagnostic**	1 (2.9)
Total	34 (100)

*Four patients from 6 lymph nodes, 2 nodular sclerosing type Hodgkin lymphoma, 1 mixed cellular type Hodgkin lymphoma, 1 diffuse large B-cell lymphoma.
**Considered malignant due to progression and diagnosis of lung adenocarcinoma in CT follow-up.

Table 4

Distribution of lymph nodes evaluated as malignant negative cytology by EBUS-TBNA according to further examination or follow-up results.

Pathology/radiology/clinical evaluation result	n (%)
Granulomatous inflammation	19 (20.2)
Reactive changes	5 (5.3)
Anthracosis findings	2 (2.1)
Lymph nodes evaluated as malignant after further examination*	7 (7.5)
Lymph nodes found to be malignant in concomitant biopsy or considered malignant due to a known diagnosis of malignancy**	21 (22.3)
Stable and benign lymph nodes in thorax CT follow-up	17 (18.1)
Lymph nodes for which further examination was recommended but could not be performed	17 (18.1)
Unable to evaluate due to failure to perform control imaging	2 (2.1)
Lymph nodes considered as tuberculosis	4 (4.3)
Total	94 (100)

CT = computed tomography.
*Six lymphomas, 1 malignant epithelial tumor metastasis.
**Patients diagnosed with malignancy from another focus by concurrent EBUS/bronchoscopic biopsy/transthoracic biopsy, patients with a previous diagnosis of known malignancy and a patient with a previous diagnosis of known malignancy, whose progression was observed although the surgical biopsy result was not diagnostic, were also included in this group.

transthoracic aspiration biopsy/bronchoscopic biopsy performed simultaneously from another station or due to a known malignancy diagnosis. In our study, a total of 28 lymph nodes

Table 5

The relationship between sensitivity and specificity according to the SUVmax cut-off value measured in PET-CT.

SUVmax cut-off value	Sensitivity (%)	Specificity (%)
2.54	98	12
3.74	96	30
4.58	92	49
5.25	90	52
6.09	85	60
6.89	74	68
7.41	61	71

SUVmax = maximum standardized uptake value.

(29.8%) whose EBUS-TBNA result was initially negative for malignancy were then evaluated as malignant. In an analysis by Marchand and Medford, data of 284 patients who underwent EBUS-TBNA were analyzed retrospectively. In this study, it was seen that 10 of 60 lymph nodes that were reported as negative for malignancy as a result of EBUS-TBNA were evaluated as malignant as a result of further investigations.[3] In a study by Demirdöğen et al in which EBUS-TBNA was applied to mediastinal and hilar lymph nodes and 406 lymph nodes in 109 patients were examined, the result of EBUS-TBNA in 93 patients was evaluated as nonmalignant. 84 of these lymph nodes were evaluated as reactive lymph nodes and surgical biopsy was performed in 9 patients. Malignancy was found in 5 of 9 patients who underwent surgical biopsy.[15] In the study conducted by Öztürk and Güllü with 483 patients, in which 1017 lymph nodes were evaluated, 465 lymph nodes were evaluated with surgical biopsy that were found to be benign with EBUS-TBNA. Among these lymph nodes, 15 were reported as malignant as a result of surgical biopsy.[10] When the data of our study and the studies in the literature are examined, it is seen that some of the lesions that were evaluated as benign as a result of biopsy taken by EBUS-TBNA were evaluated as malignant as a result of surgical biopsy or in the follow-up. This situation shows that even if the EBUS-TBNA result is considered as benign in patients examined with suspicion of malignancy, further investigations should be performed without delay in necessary patients with high suspicion of malignancy as recommended in the guidelines.[1]

In our study, the mean size of 101 (72%) benign lymph nodes measured on PET-CT was calculated as 19.19 ± 8.89 mm (6.7–70). The mean size was calculated as 29.10 ± 17.69 mm (10.9–90) in 39 (28%) lymph nodes with malignancy. In the study conducted by Wang et al, in which 124 lymph nodes of 70 patients were evaluated, the lesions were examined according to the dimensions measured in PET-CT and it was determined that 64 of the lymph nodes were malignant and 60 of them were inflammatory lymph nodes. The sizes of the lymph nodes were compared according to whether they were malignant or inflammatory. It has been reported that the mean long diameter of malignant lymph nodes is 18.7 ± 6.4 mm and the mean long diameter of inflammatory lymph nodes is 10.7 ± 3.8 mm. As a result of this study, it was observed that both long diameter and short diameter, and short-long diameter ratio of malignant lymph nodes were larger compared to inflammatory lymph nodes.[16] According to the data of our study, the size measured on PET-CT of the lymph nodes evaluated as malignant as a result of EBUS-TBNA is significantly higher than the benign ones. ($P = .0001$).

When comparing the lesions evaluated as benign and malignant in lymph nodes for SUVmax values measured in PET-CT; the mean SUVmax value of 101 lymph nodes with negative EBUS-TBNA results for malignancy was calculated as 5.63 ± 3.57 (0–19). The mean SUVmax value of 39 lymph nodes evaluated as malignant by EBUS-TBNA was calculated

as 7.87 ± 2.67 (1.9–14). Accordingly, SUVmax value measured in PET-CT was found to be higher in lymph nodes that were evaluated as malignant when compared to benign ones. (*P* = .0001) In a study conducted by Minami et al, the data of 50 patients diagnosed with lung cancer and underwent EBUS-TBNA were evaluated retrospectively. In this study, the mean SUVmax value of lymph nodes evaluated as malignant as a result of EBUS-TBNA was determined as 11.35 and the mean SUVmax value was found to be 4.75 in those evaluated as benign.[7] In the study conducted by Gan et al, 2267 lymph nodes that underwent EBUS-TBNA were evaluated and SUVmax values were examined in the groups evaluated as malignant and benign in 577 lymph nodes that PET-CT positive. According to the data of this study, the mean SUVmax value of malignant lymph nodes was 10.5 and the mean SUVmax value of benign lymph nodes was 5.99.[11] In these studies in the literature, there is a significant difference in SUVmax values between benign and malignant lymph nodes as a result of pathology. In this respect, the data obtained from our study show similarities with the existing studies.

Remarkable results were obtained when the results obtained from the lesions examined in our study and the specificity and sensitivity relationship of the SUVmax cutoff value measured in PET-CT were evaluated. First of all, in our study, in lesions evaluated as malignant as a result of EBUS-TBNA, both lesion sizes and SUVmax values in PET-CT were found to be significantly higher than benign ones. (respectively *P* = .0001, *P* = .0001) The fact that the lesions have a high SUVmax value showing FDG uptake in PET-CT and that the size of the lesion has a significant relationship with malignancy is consistent with the studies in the literature. SUVmax value and lesion size are among the primary criteria considered in malignancy evaluations.[17–19] The data obtained from our study is also in line with other studies in this respect, as expected.

The cutoff value of SUVmax in PET-CT is considered to be 2.50, which is used in malignancy studies and is significant in terms of malignancy.[20–22] According to the results of our study, when the SUVmax cutoff value in PET-CT is taken as 2.54, the sensitivity is 98%, but the specificity remains at the level of 12%. Although this value has a high accuracy for recognizing the patient group, it is seen that it is extremely insufficient to distinguish benign conditions.

In our study, when the SUVmax cutoff value in PET-CT was evaluated as 3.74, the sensitivity was 96% and the specificity was 30%. When the SUVmax cutoff value was taken as 4.58, the sensitivity was 92% and the specificity was 49%. Although there is minimal loss in sensitivity, the specificity is relatively higher at this cutoff value. Therefore, a cutoff value of 4.58 should be considered. In our study, when the SUVmax cutoff value in PET-CT was accepted as 5.25, the sensitivity was 90% and the specificity was 52%. With this cutoff value, the sensitivity as high as 90% and the specificity exceeding 50% show that the 5.25 cutoff value can be considered as an important cutoff value that can be used in malignancy studies. When the SUVmax cutoff value in PET-CT was taken as 6.09, the sensitivity was 85% and the specificity was 60%. When the SUVmax cutoff value in PET-CT is taken as 6.89, the sensitivity is 74%, the specificity is 68%; When the SUVmax cutoff value was taken as 7.41, the sensitivity was 61% and the specificity was 71%. It is observed that the specificity is increased in distinguishing benign pathologies, but there is a decrease in sensitivity when high cutoff values are used. When working with low cutoff values, false positive PET-CT results can be seen in many patients because the specificity rate is very low. When low threshold values such as the generally accepted SUVmax cutoff value of 2.5 are selected, many benign and inflammatory pathologies can cause FDG uptake at this level. These patients are also considered as PET-CT positive and evaluated as suspicious in terms of malignancy and further investigations are performed.

Since PET-CT has been an important method in malignancy research for a long time, studies are carried out to evaluate the sensitivity and specificity of PET-CT in patients who are examined for malignancy. In 2 previous studies by Hellwig et al and Bryant et al, 4.5 and 5.3 values were reported to be prominent as SUVmax cutoff values, especially in terms of distinguishing mediastinal lymph node metastases with higher accuracy.[23,24] In different recent studies, findings showing that the SUVmax value of 4, 4.31, and 5.2 increases the sensitivity and specificity in the diagnosis of malignancy.[3,7,10] In a retrospective analysis by Marchand and Medford, data of 284 patients who underwent EBUS-TBNA were retrospectively analyzed. In this study, when the SUVmax cutoff value in PET-CT was accepted as 4; the sensitivity for EBUS-TBNA was 33% in lesions with an SUVmax value of <4 and a sensitivity of 78% for EBUS-TBNA in lesions with an SUVmax value of more than 4.[3] Minami et al reported that the most appropriate SUVmax cutoff value was 4.31 in 50 patients diagnosed with lung cancer and underwent EBUS-TBNA. When the SUVmax cutoff value was accepted as 4.31, the sensitivity was evaluated as 89.80% and the specificity as 58.33%. A point mentioned about this study is that these values may be more valid for patients with adenocarcinoma. Because 36 out of 50 patients who participated in the study were diagnosed with adenocarcinoma and constitute the majority of the patient group.[7] In a comprehensive study conducted recently by Öztürk and Güllü, the diagnostic accuracy and performance of EBUS-TBNA and PET-CT in non-small cell lung carcinoma were compared. A total of 1017 lymph nodes were evaluated in the study, in which the data of 483 patients were examined. When the SUVmax cutoff value in PET-CT is accepted as 2.5, the sensitivity is 90.1% and the specificity is 29.2%; when the SUVmax cutoff value was accepted as 5.2, the sensitivity was evaluated as 74.8% and the specificity as 84.5%.[10]

As a result, in our study, 41 of 103 patients were diagnosed with EBUS-TBNA. The rate of diagnosis with only EBUS-TBNA was calculated as 39.8%. Among these, malignancy was detected in 38 patients (36.9%) and 3 patients (2.9%) were diagnosed as sarcoidosis whose pathologies were reported as granulomatous inflammation. After EBUS-TBNA, patients still in need of diagnosis were evaluated separately and further examination was performed on necessary patients. We analyzed the malignant and benign biopsy results of EBUS-TBNA lymph nodes in patients with enlargement and FDG uptake in mediastinal and hilar lymph nodes on PET-CT and the SUVmax value which shows the FDG uptake characteristics of these lesions. Considering the sensitivity and specificity rates, the cutoff values were 4.58, 5.25 and 6.09, according to the data we obtained in our investigations in order to determine different SUVmax cutoff values that can be used for higher sensitivity and specificity in malignancy studies.

Although the use of EBUS in diagnosis and staging continues to increase, it is still the gold standard surgical pathology. One of the limitations of our study may be that it was not performed with surgical pathology, but surgical samplings lag behind due to difficulties in patient tolerance, risk of complications, and cost, and the use of EBUS is becoming widespread. In addition, in our study, surgical biopsy results or follow-up data were tried to be evaluated in patients who could not be diagnosed with EBUS or whose diagnosis was suspected. Another limitation of our study is the single center data. This study may lead to the planning of multicenter studies involving more patients.

In conclusion, SUVmax cutoff values, which were prominent in our study, may be useful both in the diagnosis of malignancy and in the differentiation of benign pathologies. However, although the examinations performed in patients with malignancy are predictive in many cases, it remains an important issue to be considered in order to be able to make detailed patient-based evaluations for each patient and to carry out advanced diagnostic tests without delay. suspicion of malignancy is high.

Author contributions

Conceptualization: Erhan Ugurlu, Melis Metin.
Data curation: Erhan Ugurlu, Melis Metin, Emel Kilicarslan, Serkan Degirmencioglu, Tarik Sengoz, Ilknur Hatice Akbudak, Gamze Gokoz Dogu, Umit Aydogmus.
Formal analysis: Emel Kilicarslan, Serkan Degirmencioglu, Tarik Sengoz.
Funding acquisition: Erhan Ugurlu.
Investigation: Melis Metin, Nazli Cetin, Ilknur Hatice Akbudak.
Methodology: Erhan Ugurlu, Nazli Cetin, Melis Metin, Tarik Sengoz.
Project administration: Erhan Ugurlu.
Supervision: Erhan Ugurlu, Gamze Gokoz Dogu, Umit Aydogmus.
Visualization: Tarik Sengoz.
Writing – original draft: Erhan Ugurlu, Nazli Cetin, Melis Metin, Emel Kilicarslan, Serkan Degirmencioglu, Tarik Sengoz, Ilknur Hatice Akbudak, Gamze Gokoz Dogu, Umit Aydogmus.
Writing – review & editing: Erhan Ugurlu, Nazli Cetin.

References

[1] De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45:787–98.

[2] Lilo MT, Allison DB, Younes BK, et al. The critical role of EBUS-TBNA cytology in the staging of mediastinal lymph nodes in lung cancer patients: a correlation study with positron emission tomography findings. Cancer Cytopathol. 2017;125:717–25.

[3] Marchand C, Medford ARL. Relationship between endobronchial ultrasound-guided (EBUS)-transbronchial needle aspiration utility and computed tomography staging, node size at EBUS, and positron emission tomography scan node standard uptake values: a retrospective analysis. Thorac Cancer. 2017;8:285–90.

[4] Ong P, Grosu H, Eapen GA, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for systematic nodal staging of lung cancer in patients with N0 disease by computed tomography and integrated positron emission tomography-computed tomography. Ann Am Thorac Soc. 2015;12:415–9.

[5] Alokla K, Kheir F, Palomino J. The value of endobronchial ultrasound transbronchial needle aspiration in normal positron emission tomography in lung cancer. J Bronchology Interv Pulmonol. 2015;22:e1–2.

[6] Shingyoji M, Nakajima T, Yoshino M, et al. Endobronchial ultrasonography for positron emission tomography and computed tomography-negative lymph node staging in non-small cell lung cancer. Ann Thorac Surg. 2014;98:1762–7.

[7] Minami D, Takigawa N, Oda N, et al. Endobronchial ultrasound-guided transbronchial needle aspiration of hilar and mediastinal lymph nodes detected on 18F-fluorodeoxyglucose positron emission tomography/computed tomography. Jpn J Clin Oncol. 2016;46:529–33.

[8] Fraioli F, Kayani I, Smith LJ, et al. Positive (18)Fluorodeoxyglucose-positron emission tomography/computed tomography predicts preinvasive endobronchial lesion progression to invasive cancer. Am J Respir Crit Care Med. 2016;193:576–9.

[9] Lee J, Kim YK, Seo YY, et al. Clinical characteristics of false-positive lymph node on chest CT or PET-CT confirmed by endobronchial ultrasound-guided transbronchial needle aspiration in lung cancer. Tuberc Respir Dis (Seoul). 2018;81:339–46.

[10] Ozturk A, Gullu YT. Excellence in non-small cell lung cancer staging by endobronchial-TBNA: comparison with PET-CT and surgery. Minim Invasive Ther Allied Technol. 2019;28:213–9.

[11] Gan Q, Stewart JM, Valik E, et al. Cytologic evaluation of positron emission tomography-computed tomography-positive lymph nodes sampled by endobronchial ultrasound-guided transbronchial needle aspiration: experience at a large cancer center. Arch Pathol Lab Med. 2019;143:1265–70.

[12] Zhu R, Wang H, Lin L. Prognostic and clinicopathological value of ZWINT expression levels in patients with lung adenocarcinoma: a systematic review and meta-analysis. Clinics (Sao Paulo). 2021;76:e3222.

[13] Fielding D, Kurimoto N. Endobronchial ultrasound-guided transbronchial needle aspiration for diagnosis and staging of lung cancer. Clin Chest Med. 2018;39:111–23.

[14] Lerner AD, Feller-Kopman D. Bronchoscopic techniques used in the diagnosis and staging of lung cancer. J Natl Compr Canc Netw. 2017;15:640–7.

[15] Demirdöğen E, Ursavaş A, Aydın Güçlü O, et al. Diagnostic performance of EBUS-TBNA and its interrelation with PET-CT in patients with extra-thoracic malignancies. Tuberk Toraks. 2020;68:285–92.

[16] Wang H, Li QK, Auster M, et al. PET and CT features differentiating infectious/inflammatory from malignant mediastinal lymphadenopathy: a correlated study with endobronchial ultrasound-guided transbronchial needle aspiration. Radiol Infect Dis. 2018;5:7–13.

[17] Cohade C, Osman M, Marshall LN, et al. PET-CT: accuracy of PET and CT spatial registration of lung lesions. Eur J Nucl Med Mol Imaging. 2003;30:721–6.

[18] Langer NH, Christensen TN, Langer SW, et al. PET/CT in therapy evaluation of patients with lung cancer. Expert Rev Anticancer Ther. 2014;14:595–620.

[19] Caulo A, Mirsadraee S, Maggi F, et al. Integrated imaging of non-small cell lung cancer recurrence: CT and PET-CT findings, possible pitfalls and risk of recurrence criteria. Eur Radiol. 2012;22:588–606.

[20] Vansteenkiste JF, Stroobants SG. The role of positron emission tomography with 18F-fluoro-2-deoxy-D-glucose in respiratory oncology. Eur Respir J. 2001;17:802–20.

[21] Bryant AS, Cerfolio RJ. The maximum standardized uptake values on integrated FDG-PET/CT is useful in differentiating benign from malignant pulmonary nodules. Ann Thorac Surg. 2006;82:1016–20.

[22] Xu CC, Lei W, Jiang JH, et al. Endobronchial ultrasound-guided transbronchial needle aspiration can improve the diagnostic accuracy of positron emission tomography/computed tomography in hilar and/or mediastinal lymphadenopathy. J Cancer Res Ther. 2019;15:1490–5.

[23] Hellwig D, Graeter TP, Ukena D, et al. 18F-FDG PET for mediastinal staging of lung cancer: which SUV threshold makes sense? J Nucl Med. 2007;48:1761–6.

[24] Bryant AS, Cerfolio RJ, Klemm KM, et al. Maximum standard uptake value of mediastinal lymph nodes on integrated FDG-PET-CT predicts pathology in patients with non-small cell lung cancer. Ann Thorac Surg. 2006;82:417–22; discussion 422-3.