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Evaluation of Regional Node Involvement in The Staging of Non-small Cell Lung Cancer with F-18 FDG PET/CT

Küçük Hücreli Dışı Akciğer Kanseri Evrelemesinde Bölgesel Nod Tutulumunun F-18 FDG PET/BT ile Değerlendirilmesi

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Öz

Giriş ve Amaç: PET/BT'de küçük hücreli dışı akciğer kanserinin (KHDAK) nodal evrelemesi için mediastinal kan havuzu (MKH) aktivite eşik değerinin tanısal performansını değerlendirmek ve bölgesel nod tutulumunu değerlendirmede F-18 FDG-PET/BT'nin tanısal performansını artırabilecek değişkenleri incelemektir.
Gereç ve Yöntemler: Endobronşiyal ultrason eşliğinde transbronşiyal iğne aspirasyonu ve F-18 FDG-PET/BT uygulanan KHDAK tanılı hastalar çalışmaya dahil edildi. Lenf nodu istasyonu ve lenf nodu evrelemesinin analizi, MKH eşik değeri ile diğer beş PET/BT parametresi histopatolojik sonuçlarla karşılaştırıldı.
Bulgular: Çalışmaya 88 hasta dâhil edilmiş olup 250 lenf nodu istasyonundan patolojik örneklem yapıldı. PET/BT'de lenf nodu aktivitesinin MKH'dan yüksek olması %95.3 duyarlılık, %36.1 özgüllük, %33.1 pozitif öngörü değeri, %96.2 negatif öngörü değeri göstermiştir. İncelenen diğer beş PET/BT parametresinden nodal SUVmaks değeri ve lenf nodu/MKH SUVmaks oranı en tanısal parametrelerdi. Nodal SUVmaks için 3.8 eşik değeri %90.2 duyarlılık, %61.7 özgüllüközgüllük; lenf nodu/MKH SUVmaks oranı için 1.8 eşik değeri %90.1 duyarlılık, %60.5 özgüllük değeri göstermiştir.
Sonuç: Nodal evrelemede MKH eşik değeri ile karşılaştırıldığında daha yüksek lenf nodu/MKH SUVmaks oranı eşik değeri ve diğer PET/BT değişkenlerinin kullanılması PET/BT'nin tanısal değerini artırabilir.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, PET/BT, FDG

Abstract

Aim: To evaluate the diagnostic performance of mediastinal blood pool activity (MBP) threshold for nodal staging of non-small cell lung cancer (NSCLC) on PET/CT and to examine the variables that may improve the diagnostic performance of 18F-FDG-PET/CT in evaluating regional lymph node involvement.

Materials and Methods: The study included patients with NSCLC who underwent endobronchial ultrasound guided transbronchial needle aspiration and 18F-FDG-PET/CT. We compared the analysis of the lymph node station and staging, the MBP threshold value, and five other PET/CT parameters with the histopathological results.
Results: The study included eighty-eight patients, and collected pathological samples from 250 lymph node stations. The higher lymph node activity in PET/CT than MBP showed a sensitivity of 95.3%, a specificity of 36.1%, a positive prediction value of 33.1%, and a negative prediction value of 96.2%. Out of the five PET/CT parameters that were examined, the nodal SUVmax value and the lymph node/MBP SUVmax ratio were the most diagnostic. The 3.8 threshold value for nodal SUVmax showed a sensitivity of 90.2%, a specificity of 61.7%, and the 1.8 threshold for lymph node/MBP SUVmax ratio showed a sensitivity of 90.1%, a specificity of 60.5%.
Conclusion: When compared to the MBP threshold value in nodal staging, the diagnostic value of PET/CT may increase when a higher lymph node/MBP SUVmax ratio threshold value and other PET/CT variables are used.

Keywords: Non-small cell lung cancer, PET/CT, FDG

1. Introduction

Lung cancer is a significant contributor to global mortality rates [1]. Lymph node involvement is one of the main parts of TNM classification, which is used to stage non-small cell lung cancer (NSCLC). TNM classification is also used to figure out how the disease will progress and how long a person will live [2, 3]. Surgery is the main treatment modality in patients without distant metastasis or mediastinal lymph node involvement. While advanced mediastinal nodal disease precludes surgery, some patients with N2 disease can undergo it. Accurate nodal staging is decisive in treatment management [4, 5].

Patients with NSCLC use F-18 fluoro-2-deoxy-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) as a non-invasive imaging method to evaluate mediastinal areas and the presence of distant organ metastasis [6]. However, inflammatory or reactive processes that lead to increased FDG uptake in lymph nodes may result in a malignancy-like appearance, potentially complicating the interpretation of nodal staging. In addition, a small nodal size may be a false negative PET/CT finding. Therefore, many guidelines recommend confirming mediastinal-hilar lymph nodes with FDG uptake or large size by tissue diagnosis [7-9]. In FDG PET/CT, lesion size and maximum standardized uptake value (SUVmax) are used to evaluate lymph nodes as benign or malignant [10]. Many studies have been conducted in the literature to evaluate whether increased FDG uptake values in lymph nodes are related to disease involvement, and different threshold values have been proposed [11–13]. In a retrospective study [14], a lymph node SUVmax value greater than the mediastinal blood pool (MBP) activity value was reported as the most sensitive method. This facilitated the selection of lymph nodes for tissue sampling.

The aim of this study was to evaluate the diagnostic performance of the MBP activity threshold value in lymph node staging of non-small cell lung cancer and to investigate other variables that may improve the diagnostic performance of F-18 FDG PET/CT in evaluating regional lymph node involvement by utilizing MBP activity.

2. Materials and Methods

2.1 Patient Selection

The study included patients with suspected or diagnosed lung cancer and histopathologically confirmed NSCLC who underwent F-18 FDG PET/CT for diagnosis or staging. The study was administered in accordance with the principles of the Declaration of Helsinki, and the patients provided informed consent. Ethical approval for the study was obtained from the Ethics Committee of the Mersin Provincial Health Directorate-Mersin City Training and Research Hospital on May 10, 2023, with decision number 70.

2.2 F-18 FDG PET/CT Imaging Method

FDG-PET/CT examinations were performed on a Discovery IQ PET/CT scanner (General Electric, Waukesha, WI, U.S.A.). We asked patients to fast for at least 6 hours before PET/CT. Patients received 144 μCi/kg FDG injection via intravenous (IV) route, followed by 150 ml of saline infusion. After resting for 60 minutes, the patients were placed on the acquisition table in the supine position and prepared for whole-body oncologic PET/CT scanning. The blood glucose level of all patients was measured using a fingerstick before radiopharmaceutical administration. The maximum acceptable blood glucose level for the examination was set at ≤180 mg/dl. Non-contrast CT images were obtained from the vertex to the proximal thigh with 70 mA, 110 kV, and 0.75 mm collimation. PET images were obtained in the same position from the vertex to the proximal thigh in 7-9 beds according

to the person's height, with a count time of 2.5 minutes per bed. Non-contrast-enhanced CT data were used for iterative attenuation correction, and PET and CT images were reconstructed in axial, sagittal, and coronal planes with a thickness of 5 mm.

2.3 Tissue Diagnosis

Tissue sampling for mediastinal and hilar lymph nodes was performed by transbronchial needle aspiration (TBNA) under real-time ultrasound imaging with EBUS guidance. Lymph node selection was at the discretion of the practitioner, and three samples were taken from each lymph node. Resection surgery with lymph node dissection was performed on eligible patients. The samples obtained were delivered to the pathology laboratory.

2.4 Data Collection

In the study, the SUVmax of the MBP (MBP-SUVmax), the SUVmax of the lymph nodes (LN-SUVmax), the SUVmax of the malignant tumor (T-SUVmax), and the lymph node short diameter (LNSD) were measured, and the ratios of LN-SUVmax/MBP-SUVmax, LN-SUVmax/T-SUVmax, and LN-SUVmax/LNSD were calculated. MBP-SUVmax was measured by placing the region of interest (ROI) ring in the lumen at the level of the arcuate aorta on the PET image. LNSD was measured manually in the axial plane over the lymph node, showing FDG uptake. T-SUVmax and LN-SUVmax values were measured by manual placement of the ROI ring at the location of maximum FDG uptake on PET images. The metabolic uptake value of the lymph node with the highest SUVmax value at the lymph node station was accepted as LN-SUVmax.

Histopathologic results of lymph nodes sampled surgically or by EBUS-TBNA were recorded. Lymph nodes with a morphologically normal appearance or that were technically difficult to reach by EBUS were not sampled. TBNA tissue specimens with inadequate or indeterminate examination were considered non-malignant due to the lack of sufficient descriptive criteria. Lymph node stations were categorized based on the lymph node mapping established by the International Lung Cancer Society [15].

2.5 Statistical Analysis

FDG PET/CT was compared with histopathologic results for analysis of lymph node stations, and FDG PET/CT nodal staging was compared with histopathologic staging for analysis of lymph node staging. In the lymph node staging analysis, patients with both PET/CT and pathologic N2/3 were considered true positive; patients with PET/CT N2/3 but pathologic N0/1 were considered false positive; patients with PET/CT N0/1 but pathologic N2/3 were considered false negative; and patients with both PET/CT and pathologic N0/1 were considered true negative. For both analyses, the histopathologic results of the surgical specimen were accepted as reference in patients who underwent surgery, while EBUS-TBNA histopathologic results were accepted as reference in patients in whom surgery was not possible.

Receiver operating characteristic analysis was used to compare the diagnostic value of all parameters examined in PET/CT. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated with the determined cut-off values. Statistical analysis of the study data was performed using Statistical Package for Social Sciences (SPSS) 22.0 windows, and a p value below 0.05 was considered statistically significant.

3. Results

The study included 88 patients, and pathologic sampling was performed from 250 lymph node stations. While 182 nodal stations were sampled with EBUS-TBNA, 95 nodal stations were sampled surgically, and 27 nodal stations were sampled with both methods. Twenty-eight patients underwent surgical resection following EBUS-TBNA, and 60 patients underwent EBUS alone. PET/CT scans were performed in 58 patients before EBUS-TBNA, and 30 patients were scanned after EBUS-TBNA. Table 1 provides information about the patients.

Table 1: Patient Data

	n
Number of Patients	88
Male / Female	51 / 37
Mean Age	59,8±13,2
Age Range	27-75
Lung Cancer Pathology	
Adenocarcinoma	48
Squamous Cell Carcinoma	27
Large cell carcinoma	9
Adenosquamous Carcinoma	4

Histopathologically Evaluated Lymph Node Stations	
Right Upper Paratracheal (2R)	10
Left Upper Paratracheal (2L)	2
Right Lower Paratracheal (4R)	41
Left Lower Paratracheal (4L)	18
Subaortic (5)	9
Paraaortic (6)	6
Subcarinal (7)	65
Inferior Mediastinal (8,9)	20
Right Hilar (10R,11R)	41
Left Hilar (10L,11L)	38

Lymph node metastasis of NSCLC was detected in 54 of 182 nodal stations where EBUS-TBNA was performed, while the results of 23 lymph node stations were not diagnostic. Lymph node metastasis of NSCLC was detected in 11 of 95 surgically evaluated nodal stations. EBUS-TBNA staged 27 of the 88 patients as N2/N3 disease, while surgery staged 4 of them as well. A total of 29 patients were staged as N2/N3 disease by EBUS-TBNA or surgery.

For both the analysis of lymph node stations and the analysis of lymph node staging, lymph node activity higher than MBP activity on PET/CT had high sensitivity and negative predictive value for the detection of metastatic lymph nodes, while specificity and positive predictive value were low (Table 2). Of the 250 lymph node stations evaluated, 121 were false positives (most commonly in the left inferior paratracheal and left hilar lymph nodes), and 2 subcarinal lymph nodes were false negatives.

Table 2: Diagnostic Value of Mediastinal Blood Pool Threshold

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Lymph Node Station Analysis	95,3	36,1	33,1	96,2
Lymph Node Staging Analysis	100	21,9	38,1	100

Cut-off values of 3.8 for LN-SUVmax, 1.8 for LN-SUVmax/MBP-SUVmax, 0.19 for LN-SUVmax/T-SUVmax, and 0.36 for LN-SUVmax/LNSD (≥ 90% sensitivity). The diagnostic specificity of all cut-off values was higher than the MBP threshold value. The cut-off values for LN-SUVmax and LN-SUVmax/MBP-SUVmax had the highest specificity and lowest false positive rate (Table 3).

4. Discussion

In this study, the use of MBP activity as a cut-off value in the evaluation of NSCLC nodal staging in FDG PET/CT had a high sensitivity and negative predictive value similar to previous studies. These data allow for the direct referral of patients with PET-negative NSCLC without enlarged lymph nodes to surgery, eliminating the need for mediastinoscopy [9]. PET's low false negativity rate prevents unnecessary surgery referrals for PET-negative patients with N2/3 disease. However, when MBP activity is used as a cut-off value, a low false negative rate is accompanied by a high false positive rate, and the finding is similar to the studies [16, 17]. In our study, the specificity in lymph node station analysis was 36.1% when we accepted MBP activity as the cut-off value, compared to 72.1% in the study by Mallorie et al. [14]. The difference may stem from the fact that Mallorie et al. did not use MBP activity as a standard cut-off value in every patient, resulting in a low number of lesions undergoing EBUS-TBNA. Hwangbo et al.'s study established the MBP cut-off value at >2.5 as a criterion for lymph node malignancy, calculating a positive predictive value of 40%, which we also found to be 33.1% in our study [18]. Both studies' high negative predictive values suggest that we can use the MBP cut-off value for LN and patient selection for EBUS-TBNA.

Table 3: Diagnostic Value of Determined PET/CT Parameters

	LN-SUVmax	LN-SUVmax/MBP-SUVmax	LN-SUVmax/T-SUVmax	LN-SUVmax/LNSD
Threshold Value (≥ %90 sensitivity)	3.8	1.8	0.19	0.36
Sensitivity (%)	79.5	80.1	80.3	70.1
Specificity (%)	84.6	81.8	70.5	81.3

LN: Lymph Node, MBP: Mediastinal Blood Pool, T: Tumor, LNSD: Lymph Node Short Diameter, SUVmax: Maximum Standardized Uptake Value

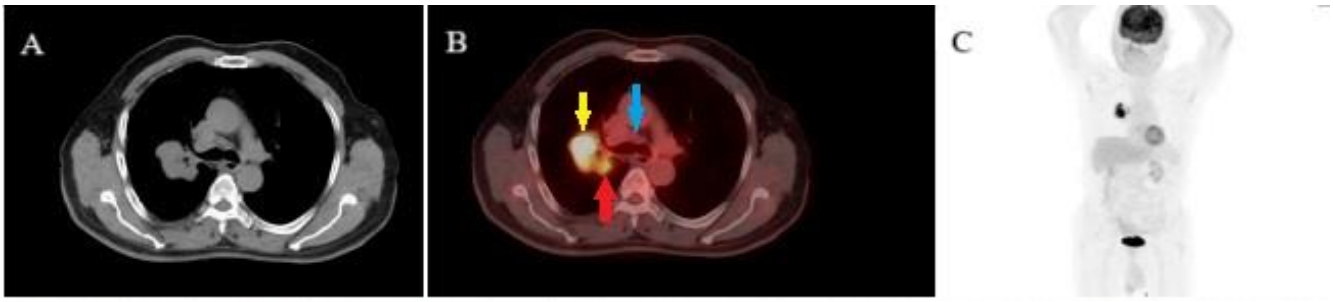

Figure 1: Computed tomography image (A), fusion PET/CT image (B)-primary malignant mass (yellow arrow), metastatic hilar lymph node (red arrow), non-metastatic precarinal lymph node (blue arrow), and MIP image (C) in a case of non-small cell lung cancer.
The metastatic hilar lymph node was confirmed to be metastatic histopathologically, with SUVmax (4.77)>MBP-SUVmax (1.28) and an LN-SUVmax/MBP-SUVmax ratio of 3.72.
SUVmax (1.64)>MBP-SUVmax (1.28), LN-SUVmax/MBP-SUVmax ratio of 1.28 in a non-metastatic precarinal lymph node was histopathologically confirmed.

In the general approach, LNSD is also measured in addition to MBP, but it is emphasized that the addition of LNSD as a parameter may complicate the situation [19, 21].

Each PET/CT parameter examined in the study was diagnostically valuable in benign or malignant lymph node differentiation. Using cut-off values of 3.8 for LN-SUVmax, 1.8 for LN-SUVmax/MBP-SUVmax, 0.19 for LN-SUVmax/T-SUVmax, and 0.36 for LN-SUVmax/LNSD, the specificity was found to be higher than the specificity for MBP (36.1%). While the determined parameters have sensitivities of approximately 90%, using a threshold value of 3.8 for LN-SUVmax reduces the false positive rate by up to 40%.

Although cut-off values cannot be compared one-to-one due to PET/CT device differences, FDG dose used, and histopathologic variables, many studies have reported that the parameters determined have diagnostic value [13, 14, 17, 22, 23]. Evison et al.'s study, which examined the diagnostic value of the N-SUVmax parameter, found 89.6% specificity and recommended a cut-off value of 4.0 [16].

Moloney et al.'s study, which used a cut-off value of 0.3 for LN-SUVmax/LNCH, found higher specificity and lower sensitivity values compared to our study [17].

Current guidelines recommend initial staging with mediastinoscopy and biopsy in patients with suspected NSCLC if mediastinal involvement is mentioned by PET/CT and surgical staging in the absence of mediastinal involvement by EBUS [7, 9, 24].

However, the selection of patients for pathologic staging should not be based solely on PET/CT parameters; the morphologic features of the lymph node, activity uptake pattern, and clinical status of the patient should also be taken into consideration, and the lowest-risk approaches that will provide the most benefit to the patient should be evaluated [25]. Although EBUS/TBNA is the first choice for tissue sampling because it is well tolerated by patients and is a minimally invasive and safe method, it has risks such as hypoxemia, bleeding, infection, and pneumothorax [26, 27]. Additionally, small or hard-to-reach lymph nodes cannot be sampled, and the patient may not tolerate the procedure [9, 28]. A low rate of false positives may help with pathologic staging when PET/CT parameters are used that are more specific than the MBP cutoff value. On the other hand, more studies are needed to assess the acceptability of the parameters in clinical practice, as an increase in specificity and a low false positive rate will be accompanied by a higher false negative rate.

The most important limitation of the study is that not all PET-positive lymph nodes with higher uptake than the activity of the MBP could be diagnosed by EBUS/TBNA due to technical difficulties. In cases where sampling with EBUS/TBNA is difficult, intervention for lymph nodes with a high probability of being positive, failure to perform surgical sampling from all lymph nodes interpreted positive by PET/CT, and false negative results that can be obtained in EBUS/TBNA are other limitations.

Also, in lymph stations with multiple lymph nodes, failure to perform a biopsy or surgical sampling of the lymph node showing the highest FDG uptake by PET/CT is also among the limitations.

5. Conclusion

Accurate staging is the most fundamental element for the evaluation of survival and the determination of treatment management in patients with NSCLC. The use of the parameters and cut-off values determined in this study may help with more accurate PET/CT interpretation and the selection of patients and lymph nodes for histopathologic sampling.

Conflict of Interest: The authors and/or their family members have no relationship with scientific committees or their members, nor do they have any affiliations with any company involving consultancy, expertise, employment, or shareholding that could potentially create a conflict of interest regarding this study.

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Author Contributions

Idea/Conception: M.K., H.A.; **Design:** M.K., H.A.; **Supervision/Consultancy:** M.K., H.A.; **Data Collection and Processing:** M.K., H.A.; **Analysis and Interpretation:** M.K., H.A.; **Literature Review:** M.K., H.A.; **Writing of the Manuscript: :** M.K.; **Critical Review:** M.K., H.A.

Consent to publish: The authors have obtained consent from the participants to publish their data.

Data availability statement: The authors declare that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes without breaching participant confidentiality.

Ethics Committee Approval:
The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study was obtained from the Ethics Committee of the Mersin Provincial Health Directorate—Mersin City Training and Research Hospital, with the decision dated May 10, 2023, and numbered 70.

Declaration of Interests: The authors declare that they have no competing interest.

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