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THE ROLE OF 18F-FDG PET-CT IN DIAGNOSIS AND PREDICTION OF PROGNOSIS IN MALIGNANT PLEURAL MESOTHELIOMA

MALIGN PLEVRAL MEZOTELYOMA AYIRICI TANISI VE PROGNOZUNDA 18F-FDG PET/BT'NİN ROLÜ

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ABSTRACT

Objective: The purpose of this study is to evaluate the performance of 18F-FDG PET/CT in the differential diagnosis of malignant and benign pleural disease as well as its prognostic value in the malignant pleural mesothelioma (MPM).

Methods: Fifty-eight patients who underwent 18F-FDG PET/CT due to diffuse or nodular pleural thickening determined on conventional CT were retrospectively analyzed.18F-FDG PET/CT scans were evaluated visually and semiquantitatively using maximum standardized uptake value (SUVmax). Mediastinal blood pool SUVmax was used as a threshold value for defining positive/negative accumulation of tracer. 18F-FDG PET/CT findings were compared with histopathological and survival data. Patients were followed up clinically/radiologically.

Results: Thirty-eight of fifty-eight patients (65.5%) had FDG (+) pleural lesions; 28/38 patients (73.6%) were diagnosed MPM and 10/38 patients (26.4%) were determined benign pleural disesase histopathologically. 20/58 scans (34.5%) were negative, and 18 of them were assumed benign based on two years follow-up, whereas 2 patients were diagnosed MPM by biopsy due to radiologic progression. Sensitivity, specificity, accuracy, positive predictive, and negative predictive values were 93%, 64%, 79%, 73%, and 90% respectively. Median overall survival was found to be 14.5 months. Higher SUVmax level (SUVmax>7.4) was associated with shorter survival (13 vs. 24 months)(p=0.032).

Conclusion: 18F-FDG-PET/CT is a sensitive imaging method for differential diagnosis of malignant/benign pleural lesions,

ÖZET

Amaç: Bu çalışmanın amacı, malign ve benign plevral hastalığın ayırıcı tanısında 18F-FDG PET/BT'nin performansı ve malign plevral mezotelyomadaki (MPM) prognostik değerini incelemektir.

Yöntem: Konvansiyonel BT'de saptanan diffüz ya da nodüler plevral kalınlaşma nedeniyle 18F-FDG PET/BT çekilen 58 hasta retrospektif olarak incelendi. 18F-FDG PET/BT taramaları, maksimum standartlaştırılmış uptake değeri (SUVmax) kullanılarak görsel ve yarı kantitatif olarak değerlendirildi. Pozitif/negatif tutulum ayrımında eşik değeri olarak mediastinal kan havuzu SUVmax değerleri kullanıldı. 18F-FDG PET/BT bulguları, histopatolojik bulgular ve sağkalım verileri ile karşılaştırıldı. Hastalar klinik ve radyolojik olarak takip edildi.

Bulgular: 58 hastanın 38'inde (%65,5) plevral lezyonlar FDG pozitifti; 28/38 hastada (%73,6) MPM ve 10/38 hastada (%26,4) benign plevral hastalık tanısı histopatolojik olarak saptandı. Negatif 20/58 taramanın (%34,5) 18'i iki yıllık takip ile benign hastalık kabul edilirken radyolojik progresyon saptanan 2 hastaya MPM tanısı kondu. Duyarlılık, özgüllük, doğruluk, pozitif prediktif ve negatif prediktif değerler sırasıyla %93, %64, %79, %73 ve %90 idi. Ortanca genel sağkalım süresi 14,5 ay olarak bulundu. Daha yüksek SUVmax düzeyi (SUVmax> 7,4), daha kısa sağkalım ile ilişkili bulundu (13 ay; 24 ay) (p=0,032).

Sonuç: 18F-FDG PET/BT, malign/benign plevral lezyonların ayırıcı tanısı için duyarlı bir görüntüleme yöntemi olup biyopsi hedefinin belirlenmesi ve hastaların yönetiminde etkilidir.

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indicates the target of biopsy, and effects the management of patients. SUVmax of MPM has a potential role for predicting the prognosis.

Keywords: Mesothelioma, PET/CT, FDG

MPM SUVmax değeri prognozu öngörme potansiyeline sahiptir.

Anahtar Kelimeler: Mezotelyoma, PET/BT, FDG

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a malignant transformation of mesothelial cells and the incidence of disease increases with occupational and environmental asbestos exposure history (1). Early and accurate diagnosis has a critical impact on the management of the disease because of its limited response to various combinations of multimodal therapy. Patients are mostly diagnosed in the advanced stage, which leads to poor overall survival (OS). Mean OS is approximately 12 months and depends on various factors, such as age, gender, and histopathological subtype (2,3). CT is the initial step for diagnosis, however, MPM cannot be differentiated from benign pleural disease occasionally, by established CT criteria (4).

18F-FDG PET/CT has been widely used for diagnosis, staging, therapy response, and prognostic information of cancer for many years with high accuracy rates. Due to the nature of the disease, malignancies generally have a higher glucose metabolism, which leads 18F-FDG PET/CT to differentiate benign from malignant disease. In literature, several studies have evaluated the differential diagnosis of 18F-FDG PET/CT in pleural disease and reported different values of sensitivity and specificity (5-8). In this regard, we evaluated the performance of 18F-FDG PET/CT in the detection of MPM as well as its prognostic value using SUVmax as a semiquantitative measure.

MATERIALS-METHODS

Patients

A total of 58 patients who underwent 18F-FDG PET/CT at our clinic between 2010- 2015 for differential diagnosis of diffuse or nodular pleural thickening determined on conventional CT were included in this retrospective study (mean age: 57 years, range: 41-77). Patients who had previous pleurodesis or invasive diagnostic procedures were excluded from the study to prevent false positive results. Demographic, clinic, and histopathological data was collected and patients were followed up until the time of death or the deadline of the study. The patient characteristics are shown in Table 1.

Table 1: Patient demographic and clinical characteristics

Age mean (range)	**58(36-77)**
Gender	
Male	n:38
Female	n:20
Histological subtype	
Epithelioid	n:9
Biphasic	n:6
Unknown	n:15
Asbestos exposure	n:11
Smoking	n:18
Asbestos+ Smoking	n:7
Basal CT Findings	
Diffuse pleural thickening	n:47
Nodulary pleural thickening	n:11
Histopathological evaluation	
Thoracentesis	n:2
Closed pleural biopsy	n:11
Medical thoracoscopy	n:5
VATS	n:30
Treatment	
Chemotherapy	n:18
Surgery	n:9
Radiation	n:3
Prognosis	
Alive	n:32
Death	n:25
Unknown	n:1

18F-FDG PET/CT Acquisition and Image Interpretation

All patients were asked to come for scanning after at least 4 hours of fasting. Images were obtained on a dedicated PET/CT scanner (Biograph TruePoint PET/CT; Siemens Healthcare. Erlangen, Germany), 60 minutes after intravenous injection of 350-450 MBq of FDG. CT acquisition was performed on a spiral CT scanner, with a slice thickness of 4 mm and a pitch of 1. After transmission scan, 3D PET acquisition was taken for 2-3 minutes per bed position for 5–8 bed positions. CT-based attenuation correction of the emission images was employed. CT-based attenuation correction of the emission images was used. PET images were reconstructed by the iterative

method using ordered-subset expectation maximization (OSEM; 2 iterations and 8 subsets). After completion of PET acquisition, the reconstructed attenuation-corrected PET images, CT images, and fused images of matching pairs of PET and CT images for review in axial, coronal, and sagittal planes and in maximum intensity projections, three-dimensional cine mode. Images were reviewed using dedicated software (Syngo, TrueD VE31A; Siemens).

Image analysis

The images were assessed visually by two board-certified nuclear medicine physicians. Areas of abnormally increased tracer uptake above the mediastinal blood pool (MBP) were defined positive and for semiquantitative analysis of metabolic activity, regions of interest (ROIs) analysis were performed for the most intense lesions on PET images.

Histopathological evaluation was performed in all FDG positive patients. Biopsy was performed to the pleural lesion with the highest FDG uptake. FDG negative patients were followed up (range:12-72 months) by contrast-enhanced CT with six-month intervals and were histopathologically examined in case of clinical or radiological progression. All false positive patients, confirmed by histopathologic examination were also followed up (range:24-36 months) with contrast-enhanced CT. Additional histopathological examinations were performed in four patients with suspicious radiological progression. The survival analysis was done to the patients with MPM.

Statistical analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. The sensitivity, specificity, and cut-off values were calculated for evaluating the clinical test. Mean OS was calculated using the Kaplan-Meier method and the influence of SUVmax on survival was assessed by log rank test. Two Independent Sample T-tests and the Mann Whitney U test were used to compare the variables between the groups. A p-value <0.05 was considered significant. Analyses were performed using commercial software (IBM SPSS Statistics 24, SPSS Inc., an IBM Co., Somers, NY).

RESULTS

According to 18F-FDG PET/CT results, 38 of 58 patients had FDG positive pleural lesions. 18F-FDG PET/CT was true positive in 28/38 patients (73.6%) whom were histopathologically confirmed as MPM (Figure 1). The histopathological subtypes were epithelioid MPM in nine patients, biphasic MPM in five patients, and the subtype data was unknown in the remaining fourteen patients. Ten patients with FDG uptake were confirmed as tuberculous pleuritis (n:4), chronic pleuritis (n:3), and non-specific inflammatory diseases (n:3) by histopathological examination (Figure 2). Additional histopathological examinations during follow-up were performed in four patients with suspicious radiological progression which was revealed as benign pathology.

No FDG uptake or lower than mediastinal blood pool uptake on pleural lesions were seen in 20/58 patients. Eighteen patients with negative scan (90%) were assumed to be true negative based on clinical and radiological follow up over two years (Figure 3). The remaining two patients were diagnosed MPM histopathologically due to progression of radiological findings during the follow up.

Diagnostic performance of 18F-FDG PET/CT in the detection of MPM was calculated as follows; sensitivity and specificity were 93% and 64%; accuracy, PPV and NPV were 79%, 73%, and 90%, respectively. The SUVmax of patients with MPM was significantly higher (median:8.53;

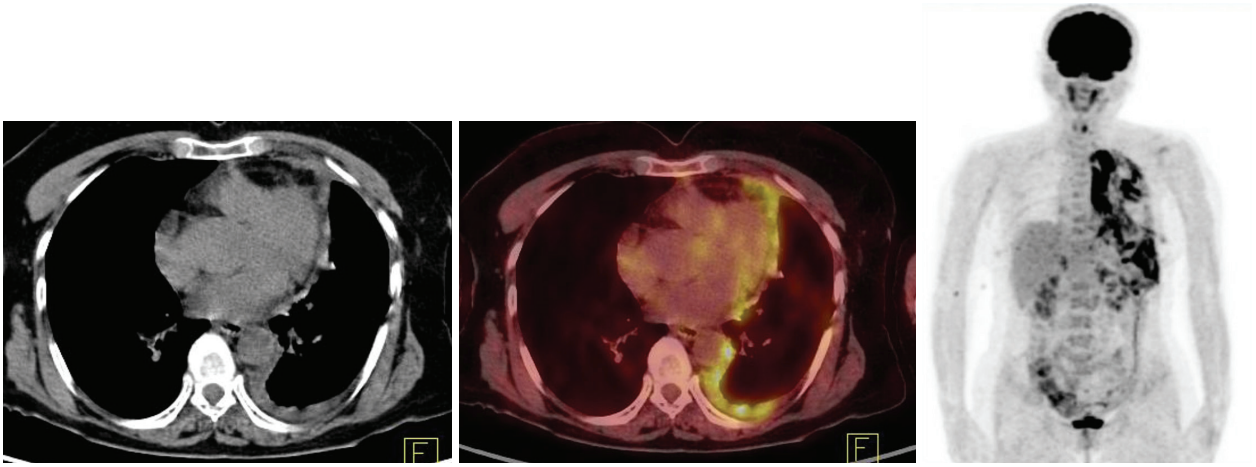

Figure 1: In CT, fusion and MIP images (a,b,c) intense FDG uptake are seen in pleural thickening of left hemithorax (SUVmax:15.6). Biopsy revealed the epithelioid type MPM.

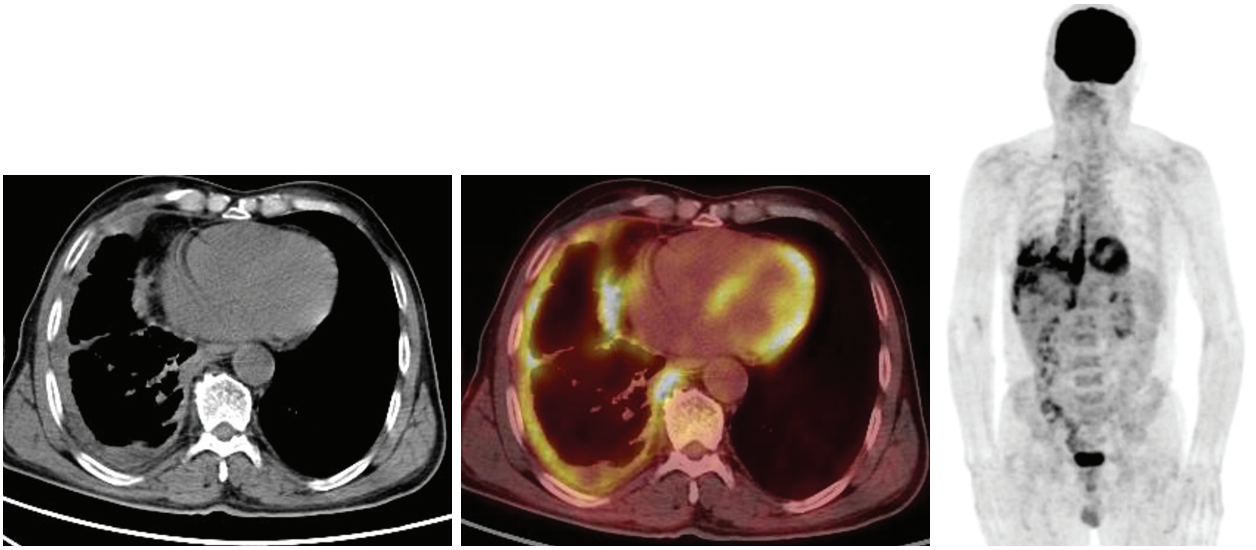

Figure 2: A false positive case which was reported suspicious for MPM based on 18F-FDG PET-CT findings was finally diagnosed as chronic pleuritis, histopathologically. In CT, fusion and MIP images (a,b,c) increased FDG uptakes are seen in pleural thickening areas of right hemithorax (SUVmax: 8,5). Patient was alive in five years follow-up without any malignant diagnosis.

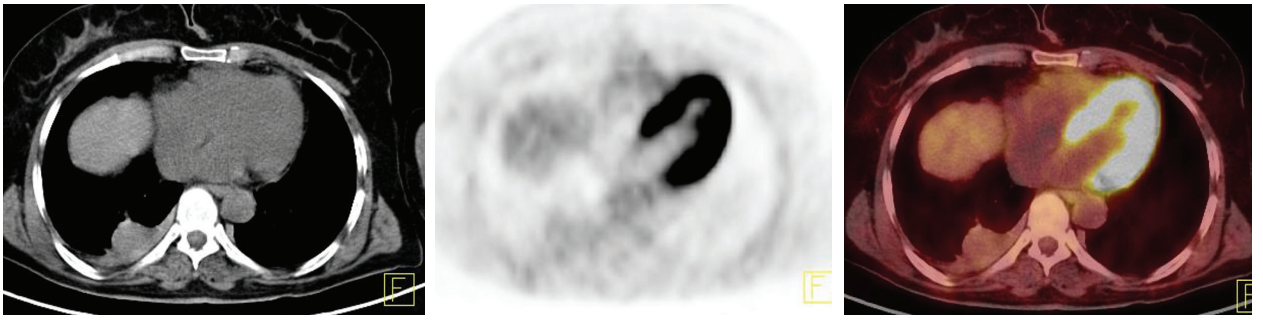

Figure 3: Extensive nodular thickening of the right pleura in CT images (a) showing no FDG uptake in PET (b) and fusion images (c) (SUVmax: 2.0). The histopathologic examination revealed benign pathology.

range:2.6-25.92) than the non-MPM patients (median:2.55; 1.5-24.73) (p=<0.01). However, the SUVmax was not significantly different between patients with epithelioid (n=9) and biphasic (n=6) MPM (p=0.111).

Median follow-up time was 26 months (range: 11.5-43.5 months, Cl%25-75) and mean OS of patients with MPM was 14.5 months. We found that higher SUVmax levels (SUVmax >7.4) were associated with shorter survival (13 months vs. 24 months p=0.032). Based on the SUVmax levels of epitheloid MPM, the mean OS was lower in tumors with higher SUVmax (SUVmax > 10) than remaining epithelioid MPM group (12 months vs. 23 months), but the statistical analysis could not be performed due to small number of patients (n:9).

The MPM staging was evaluated according to the International Mesothelioma Interest Group with 18F-FDG PET/CT, diagnostic CT-MR and histopathological findings (7). Twelve patients had stage 1-2, nine patients had stage 3, and nine patients had stage 4 disease. Nine patients were operated on, eighteen patients received chemotherapy and three patients were treated with radiotherapy. 18F-FDG PET/CT changed the therapy management in nine patients (30%) with detecting unknown distant metastases or extension to the contralateral pleura, which upstaged the patients to stage 4 disease.

DISCUSSION

MPM is a malignant transformation of mesothelial cells and has a limited response to multimodal therapy with poor prognosis. The incidence increases with occupational and environmental asbestos exposure history (1). Staging, therapeutic approach, and prognosis of MPM depend on early and correct diagnosis (9). In this regard, 18F-FDG PET/CT provides not only diagnostic information but also may predict disease outcome by using FDG uptake as a semiquantitative measure (10-13).

In our study, 28 MPM patients with pleural thickening showed mild to intense FDG uptake (>MBP) and malignancy was confirmed histopathologically. The SUVmax levels of MPM were significantly higher than the benign pleural thickening, similar with previous results (5,7). We compared the SUVmax levels of subtypes in limiting number of patients. However, we did not find any relation between the SUVmax levels of epithelioid and biphasic MPM, likewise the recent published researches (13,14).

Two patients with MPM were evaluated false negatively in 18F-FDG PET/CT due to lower FDG uptake than MBP (SUVmax:2.1-2.6). One of the false negative patients was presented with small nodular pleural thickening, while the other patient had lineer thickening. These patients were histopathologically proven to be an unknown subtype of MPM after radiological progression. We believe that, small tumor size, as well as low proliferative activity, could have caused this false negativity.

The sensitivity and the specificity were 93% and 64%; the accuracy, PPV and NPV were 79%, 73%, and 90% respectively. Abe et al. reported the sensitivity of 18F-FDG PET/CT as 100% in a large patient group (n:90) and they also emphasized the importance of the delayed images for differential diagnosis of MPM (13). A meta-analysis by Treglia et al. (n:745) reported the sensitivity of 18F-FDG PET/CT for diagnosis of MPM as 95%, which is comparable to our study (15).

In this study specificity, PPV and accuracy were 64%, 73%, 79% respectively, which is lower than previous studies (5,15,16). In the meta-analysis by Treglia et al. specificity, PPV and accuracy were 82%, 90%, and 90%, respectively. These discordant results are due to a higher number of false positive findings in our study. Granulomatous diseases such as tuberculosis are more frequently seen in Turkey which caused the majority of false positive results in our study. Elboga et al. also reported lower specificity rate for distinguishing malign and benign pleural diseases with 18F-FDG PET/CT in Turkish population as 61.5%, which is comparable to our study (6). Our findings suggest that although FDG PET/CT is a sensitive diagnostic tool in the detection of suspected pleural malignancies, it cannot replace histopathological evaluation. It is also useful for addressing the biopsy target, especially in heterogeneous tumors in order to limit false negative or insufficient results.

18F-FDG PET/CT can predict the prognosis of MPM like other malignities that FDG uptake has shown to be associated with more aggressive behavior. In several studies, a correlation between SUVmax value and survival of MPM has been reported (10-13). We also found that higher SUVmax levels (>7.4) were associated with shorter survival than other groups (13 vs 24 months, p=0.034). Although statistical analysis could not be performed due to a small number of patients, the mean OS was lower in epithelioid MPM with higher SUVmax (SUVmax>10) than remaining epithelioid MPM group (12 months vs. 23 months). Kadota et al. have described that pleomorphic subtype of epithelioid MPM known with poor prognosis was presented with high SUVmax (17). This may explain the poor prognosis of epithelioid MPM patients in our study. SUVmax can be useful for the determination of poor prognosis in epitheliod MPM when subtype of epithelioid is not determined.

The superiority and efficiency of 18F-FDG PET/CT has been reported for staging MPM especially for the assessment of stage 4 disease (18,19). In the present study, nine patients (30%) who had been potentially operable stage 2 or 3 disease were upstaged to stage 4 based on 18F-FDG PET/CT findings which prevented unnecessary surgical interventions.

The limitations of our study are the small number of MPM patients and the missing data on the subtype of MPM.

CONCLUSION

The results of our study support that 18F-FDG PET/CT is a sensitive imaging method for differential diagnosis of malignant/benign pleural lesions. 18F-FDG PET/CT can also indicate the target of biopsy and effects the management of patients by providing true staging. The SUVmax level of MPM has a role for predicting the prognosis as a noninvasive imaging marker.

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Informed Consent: Written consent was obtained from the participants.

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