Original Article

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Relationship of Plasma Cell Infiltration Rates with ^{18}F-FDG PET/CT Data and Hematological Parameters in Multiple Myeloma

Multipl Myelomda Plazma Hücre İnfiltrasyon Oranlarının ve Hematolojik Parametrelerin ^{18}F-FDG PET/CT Verileri Arasındaki İlişki

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Abstract

Objectives: This study aimed to evaluate the relationship between the degree of bone marrow involvement, hematological parameters, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG)- positron emission tomography/computed tomography (PET/CT) data in patients diagnosed with multiple myeloma.

Methods: A total of 71 patients [19 females, 52 males, mean age 67 (36-83) years] who were diagnosed with multiple myeloma between 2014 and 2021, had not received any treatment yet, and underwent ^{18}F-FDG-PET/CT for staging were included in the study.

Results: No significant correlation was observed between bone marrow standardized uptake value $(SUV)_{max}$ and plasma cell infiltration (p=0.07). However, we found that patients with visually increased bone marrow counts also had higher plasma cell infiltration rates (p=0.037). No significant correlation was found between plasma cell infiltration rates and bone marrow SUV_{max} and systemic inflammatory index (SII) (p=0.187 and p=0.446, respectively). However, there was a significant correlation between the SUV_{max} of lytic lesions showing increased ^{18}F-FDG uptake in bone and SII (p=0.025, r=0.330).

Conclusion: We believe that ^{18}F-FDG PET/CT may be an advantage over bone marrow biopsy in the diagnosis and evaluation of Multiple Myeloma recurrence and may prevent repeated bone marrow biopsies.

Keywords: Multiple myeloma, ^{18}F-FDG PET/CT, plasma cell infiltration rate, systemic immune-inflammatory index

Öz

Amaç: Bu çalışmada multipl myelom tanısı alan hastalardaki kemik iliği plazma hücre infiltrasyonu ve hematolojik parametreler ile ^{18}F-florodeoksiglukoz (^{18}F-FDG) -pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) verileri arasındaki ilişkinin değerlendirilmesi amaçlandı.

Yöntem: 2014-2021 yılları arasında multipl myelom tanısı alan, henüz tedavi almayan ve evreleme amaçlı ^{18}F-FDG- PET/BT uygulanan toplam 71 hasta [19'u kadın, 52'si erkek, ortalama yaş 67 (36-83)] çalışmaya dahil edildi.

Bulgular: Kemik iliği standartlaştırılmış alım değeri $(SUV)_{maks}$ değerleri ile plazma hücre infiltrasyonu arasında anlamlı bir ilişki bulunamadı (p=0,07). Ancak görsel olarak kemik iliği artışı olan hastalarda plazma hücre infiltrasyon oranlarının da daha yüksek olduğunu bulduk (p=0,037). Plazma hücre infiltrasyon oranları ile kemik iliği SUV_{maks} değeri ve sistemik inflamatuar indeks (SII) arasında anlamlı bir korelasyon bulunamadı (sırasıyla p=0,187 ve p=0,446). Ancak kemikte artmış ^{18}F-FDG tutulumu gösteren litik lezyonların SUV_{maks} değeri ile SII arasında anlamlı bir korelasyon vardı (p=0,025, r=0,330).

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Sonuç: Sonuç olarak MM nükslerinin tanı ve değerlendirilmesinde ^{18}F-FDG PET/BT'nin kemik iliği biyopsisine avantaj sağlayabileceğini ve tekrarlanan kemik iliği biyopsilerini önleyebileceğini düşünüyoruz.

Anahtar kelimeler: Multipl myelom, ^{18}F-FDG PET/BT, plazma hücre infiltrasyon oranı, sistemik immün-inflamatuar indeks

Introduction

Multiple myeloma constitutes 1% of all cancers and ~13% of hematological malignancies (1,2). In addition, it has been the focus of studies because it is the 2nd most common cancer type after non-Hodgkin lymphoma in hematological malignancies, and its incidence has increased by 126% from 1991 to 2016 (1,3). Multiple myeloma is a malignancy characterized by the uncontrolled proliferation of clonal plasma cells in bone marrow and by the secretion of monoclonal immunoglobulin protein (M protein) (2,3,4).

The National Comprehensive Cancer Network recommendations for staging patients with multiple myeloma at diagnosis are positron emission tomography/computed tomography (PET/CT) or whole-body low-dose CT (5).

As in many other cancers, ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET/CT is an imaging system used in staging and treatment diagnosis evaluation of hematological malignancies (6,7). ^{18}F-FDG-PET/CT is an effective method for detecting skeletal and extramedullary lesions in multiple myeloma patients (8).

We aimed to investigate the potential distribution of bone marrow plasma cell infiltration rates, PET/CT data, and hematological parameters in multiple myeloma. Thus, we aimed to determine whether ^{18}F-FDG-PET/CT can be used instead of repeated invasive bone marrow biopsy when investigating the diagnosis and recurrence of patients.

Materials and Methods

A total of 71 patients [19 females, 52 males, mean age 67 (36-83) years] diagnosed with multiple myeloma between 2014 and 2021, who had not received any treatment yet, and who underwent ^{18}F-FDG-PET/CT for staging purposes were included in the study. Our study was retrospective, and informed consent was obtained from all patients.

No patient diagnosed outside Sivas Cumhuriyet University and/or who underwent ^{18}F-FDG PET/CT at an external center were included in the study. Patients who received treatment after diagnosis or for other malignancies were also excluded.

Bone marrow aspiration results and creatinine, albumin, calcium, neutrophil, lymphocyte, beta-2 microglobulin, and platelet values were recorded from blood samples obtained within 2 weeks after the diagnosis of ^{18}F-FDG-PET/CT. The systemic inflammatory index (SII) of the patients was calculated using the neutrophil x lymphocyte/platelet formula.

Standardized uptake value maxima (SUV_{max}) values, which were calculated with ^{18}F-FDG PET/CT software in the Department of Nuclear Medicine, and the presence/absence of metastases detected by ^{18}F-FDG PET/CT were recorded.

In PET/CT image analysis, when bone lesions were evaluated, uptake greater than background bone marrow activity was considered positive. A bone marrow SUV_{max} > hepatic SUV_{max} was considered positive for diffuse bone marrow infiltration.

Approval for this study was obtained from the Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (decision no: 2022-01/21, date: 13.01.2022).

^{18}F-FDG PET/CT Imaging Protocol

Blood sugar levels of patients who remained open for a minimum of 4-6 hours were measured before the ^{18}F-FDG injection. Injection was allowed for patients whose blood sugar was below <200 mg/dL. 0.1 mCi ^{18}F-FDG per kilogram was recorded in the patients, and after being stored for 45-60 minutes, Three-dimensional PET/CT images were taken from the skull to the tip of the foot. A General Electric Discovery PET/CT 600 device was used for imaging. CT imaging, attenuation correction, and anatomical correlation were performed with a spiral 16-slice scanner at 120 kV and 172 mAs. During imaging, images were taken for approximately 2-3 min in each bed position. Axial, coronal, and sagittal fusion images were created using the Iterative reconstruction method. SUV_{max} were calculated from PET images. In the PET images, the region of interest (ROI) was placed within the primary tumor, avoiding the peripheral area. The following formula was used to calculate the SUV_{max}: [Activity in ROI (mCi/mL)×Body Weight (grams)]÷Injected Dose (mCi)

Statistical Analysis

The data obtained from our study were evaluated using SPSS 23.0 software. The normality of the data was

analyzed using the Kolmogorov-Smirnov test. Because the parametric conditions of the data were not met, the Mann-Whitney U test was used for two independent groups and the Kruskal-Wallis test for more than two independent groups. When ANOVA was used for comparisons with more than two groups, Tukey's T2 test was used to determine which group was different from the others when the homogeneity assumption was met, and Tamhane's T2 test was used when the homogeneity assumption was not met. The chi-square test was used to evaluate the data obtained by counting. The p values $\leq$0.05 were accepted statistically significant.

Results

The mean bone marrow SUV_{max} was 2.3 (range: 1-7.6). Forty-one (58%) patients had bone marrow enhancement visualized on PET/CT, whereas 30 (42%) did not. The correlation between the rates of plasma cell infiltration and the rates of visualized bone marrow enhancement was statistically significant (p=0.037). There was no significant correlation between bone marrow plasma cell infiltration rate and bone marrow SUV_{max} value (p=0.072) (Table 1). There was no significant correlation between plasma cell infiltration rates and the presence of lytic lesions with increased ^{18}F-FDG uptake >5 mm on PET/CT (p=0.05). In addition, no significant correlation was found between plasma cell infiltration rate and SUV_{max} of the lytic lesion (p=0.07).

No significant correlation was found between plasma cell infiltration rate and SII (p=0.187). No significant correlation was found between bone marrow SUV_{max} and SII (p=0.446) (Table 1). There was a significant correlation between bone lytic lesion SUV_{max} and SII (p=0.025, r=0.330). There was a significant correlation between bone marrow SUV_{max} and creatinine elevation (p=0.032) (Table 1). There was also a significant correlation between the presence of lytic lesions in bone and creatinine elevation (p=0.026). However, there was no significant correlation between the SUV_{max} of lytic lesions in bone and creatinine elevation (p=0.156). However, no significant correlation was found between bone marrow SUV_{max} and parameters such as platelet, hemoglobin, calcium, beta- 2 microglobulin, and albumin (p=0.977, p=0.806, p=0.505, p=0.216, p=0.423, respectively) (Table 1).

Discussion

No significant correlation was found between plasma cell infiltration rate. The presence of bone marrow involvement and the extent of extramedullary tissue involvement are important factors affecting the prognosis and clinical management of patients with multiple myeloma.

In their study, Sager et al. (9) found a significant correlation between bone marrow biopsy cellularity, plasma cell ratio, and bone marrow SUV_{max}. In conclusion, the correlation between bone marrow SUV_{max} and plasma cell ratio suggested that PET/CT could prevent repeated bone marrow biopsies during follow-up.

Ak and Gulbas (10) showed that increased ^{18}F-FDG uptake in the bone marrow of patients with multiple myeloma was associated with the percentage of plasma cell infiltration in the bone marrow. Therefore, the authors stated that the ^{18}F-FDG-PET/CT study may be a valuable tool for estimating the levels of myeloma cells in bone marrow, and it is an imaging method that can be used in response to treatment and follow-up of patients.

However, our study found that plasma cell infiltration rates were also high in patients with visually increased bone marrow. Still, we did not find any significant correlation between bone marrow SUV_{max} and plasma cell infiltration rates. This may be due to the limited number of patients or the individual differences in the fields on which we based the bone marrow SUV_{max} levels.

Cengiz et al. (11) in their study, no correlation was found between the ^{18}F-FDG uptake rate of bone marrow and calcium, albumin, and beta-2 microglobulin levels, which is consistent with our study.

However, a significant correlation was observed between the ^{18}F-FDG uptake rate in bone marrow and creatinine elevation. In addition, the presence or absence of lytic lesions in bone was significantly correlated with creatinine elevation. This is related to disease aggressiveness.

According to Kim et al., (12), regarding hematological parameters, a high neutrophil-to-lymphocyte ratio, low

Tables 1. The relationship between bone marrow SUV_{max} levels and hematological and biochemical parameters

	Plasma cell infiltration rate/ SUV_{max}	SII/ SUV_{max}	Platelet/ SUV_{max}	Hemoglobin/ SUV_{max}	beta-2 microglobulin/ $SUVm_{ax}$	Calcium/ SUV_{max}	Creatinine/ SUV_{max}	Albumin/ SUV_{max}
r	0.215	0.93	0.04*	-0.03	0.153	0.083	-0.567	0.101
p	0.07	0.446	0.977	0.806	0.216	0.505	0.03*	0.423

SUV_{max}: Maximum standardized uptake value, *= p< 0.05, SII: Systemic inflammatory index

platelet count, and high c-reactive protein were found to be independently negatively associated with overall survival. In a study by Shi et al., (13) high neutrophil-to-lymphocyte ratio and low platelet-to-lymphocyte ratio were compatible with poor prognostic clinical results and suggested their utility as prognostic biomarkers.

Recently, the systemic inflammation index (SII) based on peripheral platelet, neutrophil, and lymphocyte counts has been shown to be a promising prognostic indicator in various diseases.

In our study, there was a significant correlation between SII and the SUV_{max} value of the lytic lesion in the bone (p=0.025, r=0.330). Many studies have reported that high tumor lesion SUV_{max} and SII values increase tumor aggressiveness and poor prognosis (14,15,16). For this reason, we believe that we found a correlation between bone lesion SUV_{max} and SII values in our study. We believe that patients with a high lesion SUV_{max} value will also have a high SII and a worse prognosis. Therefore, it should be kept in mind that anti-inflammatory therapies may be added to such patients during follow-up. The most important limitation of our study is that we could not reach the targeted number of patients and could not evaluate the prognosis of the patients.

Conclusion

No significant correlation was observed between bone and bone marrow uptake and bone marrow plasma cell infiltration rate on ^{18}F-FDG PET/CT. However, our study found that patients with visually increased bone marrow uptake also had high plasma cell infiltration rates. In conclusion, we believe that ^{18}F-FDG PET/CT may be an advantage of bone marrow biopsy in the diagnosis and evaluation of the recurrence of multiple myeloma and may prevent repeated bone marrow biopsies.

In addition, our study showed a significant correlation between the SUV_{max} of lytic lesions in bone and SII (p=0.025, r=0.330). Therefore, we believe that the prognosis will worsen as the SUV_{max} of lytic lesion increases.

In addition, increased serum creatinine levels were associated with bone marrow SUV_{max}. We believe this is also related to the aggressiveness of the disease and poor prognosis.

We found 4 studies investigating the relationship between ^{18}F-FDG-PET/CT parameters and bone marrow plasma cell infiltration rate in multiple myeloma. Although the number of patients included in these studies was insufficient, we believe that further studies would be useful to provide an advantage to bone marrow biopsy, an invasive method for the diagnosis and follow-up of multiple myeloma. In this regard, we believe that our study results are valuable.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (decision no: 2022-01/21, date: 13.01.2022)..

Informed Consent: Our study was retrospective, and informed consent was obtained from the patients.

Footnote

Authorship Contributions

Surgical and Medical Practices: H.T., Concept: Z.H., Design: Z.H., Data Collection or Processing: Z.H., Analysis or Interpretation: Z.H., Ö.U.B., H.T., Literature Search: Ö.U.B., Writing: Ö.U.B.

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