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Characteristics of Radiopharmaceutical Uptake in Primary Tumor and Metastatic Lesions of Prostate Carcinoma: Comparison of Oligometastatic with Multimetastatic Disease

Prostat Kanserinin Primer Tümör ve Metastatik Lezyonlarında Radyofarmasötik Tutulumunun Karakteristikleri: Oligometastatik ve Multimetastatik Hastalıkların Karşılaştırılması

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Abstract

Objectives: Oligometastases may generate secondary to indolent tumor biology. In this study, we investigated whether semiquantitative measures of ^{18}F-fluorodeoxyglucose (FDG) and gallium-68 (^{68}Ga) prostate-specific membrane antigen (PSMA) uptake of metastatic lesions and prostatic sites are different between oligometastatic (OM) and multimetastatic (MM) disease of prostate carcinoma (PC). **Methods:** Patients with PC, who underwent positron emission tomography/computed tomography (PET/CT) from October 2012 to February 2020 were retrospectively reviewed. Patients, whose reports were consistent with metastatic diseases were selected. Patients classified as with MM or OM disease. Maximum standardized uptake values (SUV_{max}) were calculated from metastatic lesions and the prostatic site. The median of the SUV_{max} results between patients with OM and MM disease were compared. **Results:** A totally 145 patients with a mean age of 71.46±9.26, were evaluated. In 59 of 145 patients, ^{18}F-FDG PET/CT was performed; 86 patients had gone through ^{68}Ga PSMA PET/CT. Thirty-seven of 145 patients were OM, whereas 108 patients were MM. The median of the SUV_{max} of metastatic lesions in patients with OM and MM disease in the ^{18}F-FDG group were 5.60 and 9.51, respectively. The results of the calculated median SUV_{max} values in OM and MM disease in the Ga-68 PSMA group were 13.44 and 29.84, respectively. A significant difference was observed in the median SUV_{max} results of metastatic lesions between OM and MM disease ($p<0.05$). Median values of SUV_{max} calculated from the prostatic site in OM and MM disease were 7.83 and 12.29 respectively in ^{18}F-FDG; 26.23 and 26.74 in the ^{68}Ga PSMA group. No significant difference was found in the SUV_{max} results of the prostatic site between OM and MM disease ($p>0.05$). **Conclusion:** SUV_{max} results of metastatic lesions are significantly higher in patients with MM than in patients with OM disease in patients with PC, which may be secondary to their different biological contents in terms of aggressiveness.

Keywords: Oligometastasis, prostate carcinoma, SUV_{max}, PET/CT

Öz

Amaç: Oligometastazlar, tümörün sınırlı metastatik kapasitesini ifade etmekte olup hastalığın yavaş biyolojisine sekonder gelişebildikleri düşünülmektedir. Bu çalışma, prostat kanserinde (PK) prostat bölgesi ve metastatik lezyonların ^{18}F-florodeoksiglukoz (FDG) ve galyum-68 (^{68}Ga) prostat spesifik membran antijeni (PSMA) tutulumunun semikantitatif ölçümlerinin oligometastatik (OM) ve multimetastatik (MM) hastalık arasında farklı olup olmadığını araştırmak için tasarlanmıştır.

Yöntem: Ekim 2012-Şubat 2020 tarihleri arasında pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) incelemesi yapılan PK'li hastaların verileri retrospektif olarak incelendi. Sonuç raporları metastatik hastalık ile uyumlu olan hastalar seçildi. Hastalar MM veya OM hastalığı olanlar olarak iki gruba

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ayrıldı. İlgi alanı, görsel olarak en yüksek radyofarmasötik tutulumu gösteren metastatik lezyondan ve prostat bölgesinden çizilerek maksimum standartlaştırılmış tutulum değerleri (SUV_{maks}) hesaplandı. OM ve MM'li hastalarda prostat bölgesi ve metastatik lezyonların medyan SUV_{maks} değerleri karşılaştırıldı.

Bulgular: Yaş ortalaması 71,46±9,26 olan, 47-90 yaş aralığında toplam 145 hasta değerlendirildi. Yüz kırk beş hastanın 59'una ^{18}F-FDG PET/BT uygulandı; kalan 86 hastaya ^{68}Ga PSMA PET/BT incelemesi yapıldı. Yüz kırk beş hastanın 37'si OM, 108 hasta MM hasta grubundaydı. ^{18}F-FDG uygulanmış OM ve MM hastalığı olan hastalarda metastatik lezyonların medyan SUV_{maks} değeri sırasıyla 5,60 (aralık: 1,72-17,40) ve 9,51 (aralık: 4,13-56,01) olarak hesaplandı. ^{68}Ga PSMA grubundaki OM ve MM hastalığı olanlarda hesaplanan metastatik lezyondan hesaplanan medyan SUV_{maks} değerleri sırasıyla 13,44 ve 29,84 olarak bulundu. ^{18}F-FDG ve ^{68}Ga PSMA gruplarında OM ve MM hastalığı olan hastaların metastatik lezyonlarının medyan SUV_{maks} değerleri istatistiksel olarak anlamlı fark gözlenirken ($p<0,05$), prostat bölgesinden hesaplanan medyan SUV_{maks} değerleri ^{18}F-FDG grubunda sırasıyla 7,83 ve 12,29; ^{68}Ga PSMA grubunda ise 26,23 ve 26,74 olarak bulundu ve aralarında istatistiksel olarak fark saptanmadı ($p>0,05$).

Sonuç: Prostat kanserinde metastatik lezyonların SUV_{maks} değerleri MM hastalarda OM hastalardan anlamlı olarak daha yüksek olup bu sonuç, OM ve MM yayılım gösteren tümörlerin agresiflik açısından farklı biyolojik içeriklerinden kaynaklanıyor olabilir.

Anahtar kelimeler: Oligometastaz, prostat kanseri, SUV_{maks}, PET/BT

Introduction

Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is overexpressed in prostate carcinoma (PC) (1). Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in most primary and metastatic lesions (2). Expression levels of PSMA are directly associated with PC aggressivenessand with higher expression in higher-grade and metastatic castration-resistant disease (1).

The correct staging of PC is important for treatment planning and patient management. Positron emission tomography/computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (FDG) is the standard imaging modality for staging, restaging, and the evaluation of therapy response in various tumors. Besides enabling visual interpretation, this modality gives quantitative information about the level of metabolic activity and biological aggressiveness of the tumor by calculating the degree of ^{18}F-FDG uptake known as the standardized uptake value (SUV). In PC, however, due to the reported less than favorable results than those from other cancer, the role of ^{18}F-FDG PET/CT is not well recognized (3). Recently, gallium-68 (^{68}Ga) labeled PSMA ligands for PET imaging have been introduced and ^{68}Ga PSMA is the most abundantly used agent for PSMA-targeted PET imaging. High diagnostic sensitivity and high accuracy for detecting metastases of ^{68}Ga-PSMA PET/CT in PC have been well established (2,4). Like in ^{18}F-FDG PET/CT, a three-dimensional distribution of ^{68}Ga PSMA is produced, and quantitative measures allowing non-invasive assessment of PSMA expression can be calculated.

It has been reported that the number and location of metastatic sites impact survival in patients with PC (3). Observing worse outcomes for the increasing number of nodal and distant metastases and obtaining remission or possibly cure using intensive treatment in patients with a limited number of metastatic site, introduced the concept of oligometastatic (OM) disease in the PC armamentarium (5,6). Besides clinical diagnosis, the biological component of this entity has also been an area of interest; questions looking for an answer whether the tumors that cause the OM disease might be biologically different from those that induce multimetastatic (MM) lesions or the entity is improved detection of existing distant metastatic disease because of more sensitive imaging modalities or not, have been arisen (7).

Recently, a significant correlation with the grade group of the primary tumor and SUV values was shown, higher SUV results in higher Gleason scores (GS) of 8 and 9, were observed in patients with PC with ^{68}Ga PSMA PET/CT imaging (8). Taking from this point, we wanted to investigate whether semiquantitative measures of ^{18}F-FDG and Ga-6 PSMA uptake differs or not between OM and MM disease in patients with PC.

Materials and Methods

Patients

Data of patients with prostate adenocarcinoma who underwent ^{18}F-FDG or ^{68}Ga PSMA PET/CT imaging between October 2012 and February 2020 in Selcuk University Medical Faculty Department of Nuclear Medicine, were retrospectively reviewed. Patients, whose reports were consistent with metastatic diseases, were selected. The study was approved by the Selcuk University Faculty of Medicine Ethics Committee (meeting date: 25.12.2019, decision number: 2019/382), and written informed consent was obtained in all patients under our institution's rules.

^{18}F-FDG and ^{68}Ga-PSMA PET/CT Imaging

PET/CT body images were taken using an integrated scanner (Biograph mCT, Siemens, Germany). First, low-dose unenhanced CT using the 16 slice CT with acquisition parameters of 190 mA, 5 mm slice thickness, and 140

kV was performed for attenuation correction. Then, PET emission scanning in 8 or 9 bed positions with an acquisition time of 3 min per bed position from the skull base to the mid-thigh was acquired. For ^{18}F-FDG PET/CT imaging, all patients were asked to fast at least 6 h before the scanning, and blood sugar levels were confirmed to be lower than 200 mg/dL. All acquisitions were performed 60 min after the intravenous administration of 370 MBq ^{18}F-FDG and 1.8-2.2 MBq per kilogram/bodyweight of ^{68}Ga PSMA.

Image Interpretation and Semi Quantification

PET/CT images were analyzed and semiquantitative calculations of ^{18}F-FDG uptake and ^{68}Ga PSMA expression were performed on a Siemens Syngo.via PET/CT workstation. Images were analyzed regarding primary lesions and extraprostatic metastases. Radiopharmaceutical uptake higher than the surrounding background activity and distinct from physiologic sites were pathologic. In patients with solitary lesions showing radiopharmaceutical uptake, confirmation of metastases was performed with additional modality including CT or magnetic resonance imaging. Patients with metastatic disease were included in the study while the ones with synchronous tumors were excluded. Patients are then further classified as with MM or OM disease. OM disease was defined as having 3 or fewer metastases as suggested in the literature (9). Patients with more than 3 metastatic sites were classified as MM. Besides visual interpretation, semiquantitative analysis was performed in all patients by a single nuclear medicine physician. Region of interest (ROI) was drawn manually around the prostate gland or prostate site in those previously operated. In all patients, for the quantification of metastatic disease, ROI was drawn over the visually most radiopharmaceutical avid metastatic lesion to calculate the maximum SUV (SUV_{max}), which was normalized to body weight. Sites of physiological uptake were manually excluded while drawing ROI, and SUV_{max} values were noted. In both OM and MM patients, after noting the SUV_{max} values of the lesions, the highest value among them was considered for statistical analysis, for both radiopharmaceuticals. Clinical data of patients including GS and previous therapy history, were also collected from the files of the patients and the information system of our hospital.

Statistical Analysis

For statistical analyses, the software package SPSS v16.0 was used. Results of SUV_{max} were expressed as a median. Mann-Whitney U test was used to compare the SUV_{max} results of patients with OM and MM disease. Fisher's exact test was used for comparing frequency distributions between groups. Statistical analyses were performed separately in the calculation the significance of semiquantitative results for two different radiopharmaceuticals. The results were evaluated at the 95% confidence interval, and the significance level was taken as 0.05.

Results

A total of 145, age range 47-90 years with a mean age of 71. 46±9.26, were evaluated. In 59 of 145 patients (41%), ^{18}F-FDG PET/CT was performed; the remaining 86 (59%) patients had gone through ^{68}Ga-PSMA PET/CT examination. Thirty-seven of 145 patients (26%) were OM (Figures 1, 2). In 17 of these 37 patients, ^{18}F-FDG was used as a radiopharmaceutical, and in the remaining 20, ^{68}Ga PSMA was injected. The remaining 108 patients were MM (Figures 3, 4); 42 were in the ^{18}F-FDG group and 66 were in the group of ^{68}Ga PSMA.

Among all OM patients, 17 showed (46%) only bone metastases, 13 of 37 (35%) had lymph node metastases, and in 3 patients (8%) only soft tissue metastases including liver, lung, and the suprarenal gland was observed. In the same group with OM disease, bone and lymph node and bone and soft tissue metastases were seen in 3 (8%) and 1 (3%) patients, respectively. For both radiopharmaceuticals, in the OM group, metastatic disease was limited to the

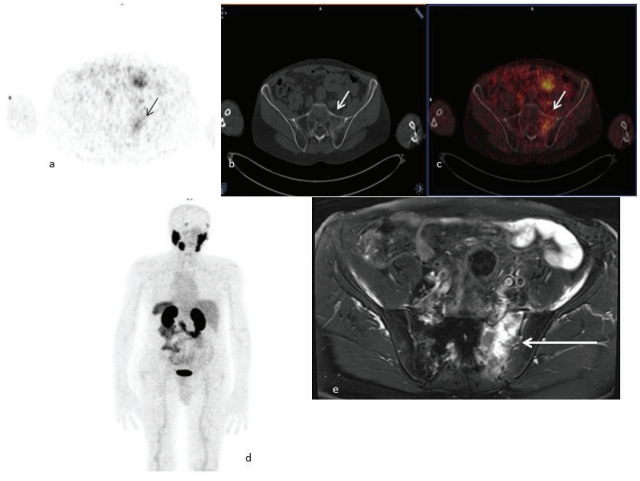

Figure 1. Transaxial (a: PET, b: CT, c: fused) and MIP (d) ^{68}Ga PSMA PET/CT images of a 42 year old patient with GS of 10. This patient, whose images depicted increased radiotracer accumulation and heterogeneous density in the left part of sacrum (a, b and c, respectively; arrows), was classified as oligometastatic. Calculated SUV_{max} of the bone lesion was found as 7.26. Magnetic resonance imaging also revealed metastatic lesion in left part of sacrum with contrast enhancement (e, arrow)
PET: Positron emission tomography, CT: Computed tomography, ^{68}Ga: Gallium-68, PSMA: Prostate-specific membrane antigen, GS: Gleason scores, SUV_{max}: Maximum standardized uptake value, MIP: Maximum intensity projection

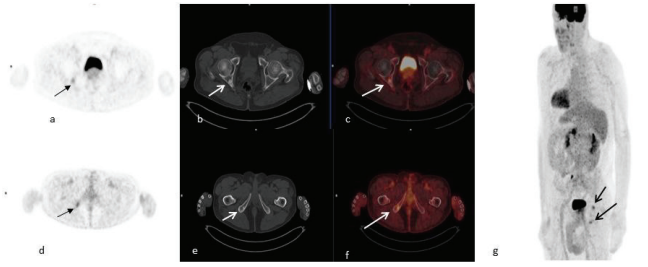

Figure 2. Transaxial (a-d: PET, b-e: CT, c-f: fused) and MIP (g) ^{18}F-FDG PET/CT images of a 69 year old oligometastatic patient with GS of 6. Sclerotic metastatic bone lesions were seen in the inferior part of right acetabulum and right ischium (b-e, arrows) with increased radiotracer uptake (a, c, d, f, g, arrows). SUV_{max} of the lesion in acetabulum was calculated as 5.35

PET: Positron emission tomography, CT: Computed tomography, FDG: Fluorodeoxyglucose, GS: Gleason scores, SUV_{max}: Maximum standardized uptake value, MIP: Maximum intensity projection

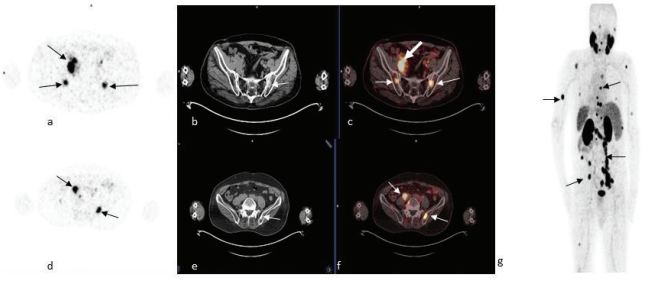

Figure 3. Transaxial (a-d: PET, b-e: CT, c-f: fused) and MIP (g) ^{68}Ga PSMA PET/CT images of a 79 year old mulitmetastatic patient with GS of 7, revealed metastatic lymph nodes and sclerotic bone metaseses (b-e, arrows) with increased radiopharmaceutical uptake (a, c, d, f and g, arrows). SUV_{max} of the right parailiac lymph node was calculated as 57.18 (c, thick arrow)

PET: Positron emission tomography, CT: Computed tomography, ^{68}Ga: Gallium-68, PSMA: Prostate-specific membrane antigen, GS: Gleason scores, SUV_{max}: Maximum standardized uptake value, MIP: Maximum intensity projection

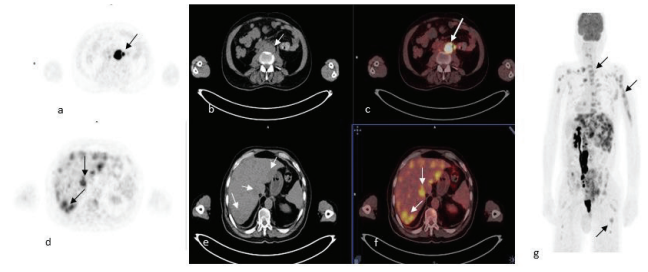

Figure 4. Transaxial (a-d: PET, b-e: CT, c-f: fused) and MIP (g) ^{18}F-FDG PET/CT images of a 77 year old patient. Multimetastases including bone (g, arrows), paraaortic lymph nodes (a, b, c, arrows) and liver (d, e, f, arrows) with increased ^{18}F-FDG uptake were observed. Calculated SUV_{max} of lymph node was found as 56. 01 (c, arrow)

PET: Positron emission tomography, CT: Computed tomography, FDG: Fluorodeoxyglucose, SUV_{max}: Maximum standardized uptake value, MIP: Maximum intensity projection

pelvic region involving the pelvic bones and/or nodes in 25 of 37 (68%) patients. The most common sites of bone metastases were pelvic bones followed by the vertebrae (60% and 27%, respectively) in patients with OM patients. In MM patients, on the other hand, only bone metastases were observed in 33 of 108 patients (31%), only lymph node metastases were seen in 17 of them (16%), and only soft tissue metastases were present in 2 (2%). In the remaining 56 patients with MM disease, bone and lymph node, bone and soft tissue, and metastatic disease involving all mentioned sites were noted except 1 patient in whom only lymph node and soft tissue metastases were seen. Taken together, the bone was the most common site of extraprostatic metastases in patients with both OM and MM disease (57% and 81%, respectively). The highest SUV_{max} was noticed in lymph node metastases in all patients except ones in OM disease of the ^{18}F-FDG group. The distribution of metastatic sites in patients with OM and MM disease and SUV_{max} results of metastatic lesions are detailed in Tables 1, 2.

The median of the SUV_{max} of metastatic lesions in OM and MM patients in the ^{18}F-FDG group was 5.60 (range: 1.72-17.40) and 9.51 (range: 4.13-56.01), respectively. The results of the calculated median SUV_{max} values in OM and MM patients in the ^{68}Ga PSMA group were 13.44 (range: 3.72-60.34) and 29.84 (range: 4.29-88.80), respectively. Statistically, a significant difference was observed in the median SUV_{max} results of metastatic lesions between patients with OM and MM disease for both radiopharmaceuticals (p=0.0001 and p=0.009 for ^{68}Ga PSMA and ^{18}F-FDG respectively, Mann-Whitney U test). Thirty-one of 86 patients (86%) in the ^{68}Ga PSMA group were *de novo* patients with PC (9 were OM, 22 were MM patients). The remaining ones were patients in whom therapy including, surgery, radiotherapy, or systemic therapy was used previously (11 were OM, 44 were MM patients). In the ^{18}F-FDG group, 12 of 17 OM patients were *de novo* PC, 5 patients were admitted at the post-therapy state; whereas 18 patients in MM disease had *de novo* PC and 24 of them were imagined after therapy. The presence of patients in the post-therapy state negatively affected the accumulation of the radiopharmaceutical in the prostate site that in the OM group; only 11 of 20 and 6 of 17 patients showed an accumulation of ^{68}Ga PSMA and ^{18}F-FDG, respectively. Similarly, in the MM group, 33 of 66 and 13 of 42 patients had radiopharmaceutical uptake for ^{68}Ga PSMA and ^{18}F-FDG, respectively, in the prostate site. Median values of SUV_{max} calculated from the prostate site in patients with OM (range: 4.05-15.54) and with MM disease (range: 5.89-34.37) were 7.83 and 12.29 in the

Table 1. Distribution of metastatic sites in all patients with OM and MM disease

	Site of metastases							
Type of metastases	**Bone only**	**Lymph node only**	**Soft tissue only**	**Bone + lymph node**	**Bone + soft tissue**	**Bone + soft tissue + lymph node**	**Soft tissue + lymph node**	**Total**
OM	17	13	3	3	1	-	-	37
MM	32	15	2	40	6	12	1	108
Total	49	28	5	43	7	12	1	145

OM: Oligometastatic, MM: Multimetastatic

Table 2. Results of median SUV_{max} values of radiopharmaceutical avid metastatic lesions in patients with OM and MM disease

Site of metastases	Patients with OM disease in ^{18}F-FDG group (n=17)	Patients with MM disease in ^{18}F-FDG group (n=42)	Patients with OM disease in ^{68}Ga-PSMA-11 group (n=20)	Patients with MM disease in ^{68}Ga-PSMA-11 group (n=66)
Lymph node	5.20	10.01	21.86	36.80
Soft tissue	6.20	9.20	17.13	18.57
Bone	5.35	8.15	11.48	27.65

n: Number, SUV_{max}: Maximum standardized uptake value, OM: Oligometastatic, MM: Multimetastatic, ^{68}Ga: Gallium-68, FDG: Fluorodeoxyglucose, PSMA: Prostate-specific membrane antigen

^{18}F-FDG group, respectively. In the ^{68}Ga PSMA group, on the other hand, nearly the same median SUV_{max} values were reached in the prostate sites such as 26.23 and 26.74 in patients with OM (range: 5.96-122.04) and with MM disease (range: 8.34-76.15), respectively. Although a higher value was calculated in MM disease for ^{18}F-FDG, no statistically significant difference was found in the SUV_{max} results of the prostate site between patients with OM and MM disease (p=0.136, Mann-Whitney U test). The results of semiquantifications of prostatic uptake and metastatic lesions in patients with MM and OM disease according to the radiopharmaceutical are summarized in Table 3.

When we looked for associating OM and MM disease with GS, we could not reach the scores of 13 patients in the ^{68}Ga-PSMA group, 1 in OM, and 12 in MM patients. In the ^{18}F-FDG group, GS of 14 patients were not available, 3 in OM and 11 in MM patients. For both radiopharmaceuticals, there were 45 patients with GS of <7 and 73 patients' GS was ≥7. The distribution of the patients according to the metastatic stage was 14 (31%) and 31 (69%) for OM and MM disease, respectively, in GS <7 patients. Among patients with GS above, 19 of them (26%) had OM and 54 (74%) had MM disease. No statistically significant difference was observed in the frequency distributions of OM and MM disease between patients with GS <7 and with GS ≥7 (p=0.673, Fisher's exact test). The distribution of the patients according to GS and type of metastases for the two radiopharmaceuticals is shown in Table 4.

Table 3. Median SUV_{max} values calculated from prostatic site and metastatic lesions in all patients for two radiopharmaceuticals (range in parenthesis)

	^{68}Ga PSMA		^{18}F-FDG	
	Prostatic site	**Metastatic lesion**	**Prostatic site**	**Metastatic lesion**
OM	26.23 (5.96-122.04)	13.44 (3.72-60.84)	7.83 (4.05-15.54)	5.60 (1.72-17.40)
MM	26.74 (18.34-76.15)	29.84 (4.25-88.80)	12.29 (5.89-34.37)	9.51 (4.13-56.01)
p value (95% CI)	*	0.0001	0.136	0.009

*Statistical significance between the results of ^{68}Ga PSMA uptake of prostatic site in patients with OM and MM disease was not analyzed because of the nearly same results observed. CI: Confidence interval, ^{68}Ga: Gallium-68, FDG: Fluorodeoxyglucose, PSMA: Prostate-specific membrane antigen, OM: Oligometastatic, MM: Multimetastatic

Table 4. Distribution of the patients according to GS and type of metastases of patients with available score

	Type of metastases		
GS	**OM**	**MM**	**Total**
<7	14	31	45
≥7	19	54	73
Total	33	85	118*

*GS scores of 4 patients with OM disease and 23 patients with MM disease were not available. GS: Gleason score, OM: Oligometastatic, MM: Multimetastatic

Discussion

The improvements in localized therapies that ablate the limited amount of metastatic disease and can even cure some patients highlighted once more the practical significance of the OM paradigm, which was first proposed in 1995 (10). Moreover, data suggesting the distinct biological differences between limited metastatic lesions and widely disseminated disease which is also supported by their different clinical settings for multiple primary cancers, including that of the prostate, have emerged (11).

Although no consensus exists, OM disease is generally defined as less than or equal to five metastatic sites on conventional imaging, including bone scintigraphy and CT, in patients with PC (7). Because of their limited sensitivities, which are in the 60%-80% range for a bone scan and 70%-80% for the CT, the functional imaging modality of PET/CT, which offers the ability to evaluate tumor metabolism with several radiotracers, have been increasingly used for detecting of PC metastases (3). It has been shown that ^{18}F-FDG PET/CT, may be useful in the diagnosis and staging of aggressive primary prostate tumors (12). The ability of ^{18}F-FDG PET/CT in the detection of metastatic disease in patients with biochemical failure and negative conventional imaging studies has been emphasized (12). Being highly specific, ^{68}Ga PSMA has been suggested as a new radiopharmaceutical that can detect prostate cancer relapses and metastases (2). The diagnostic sensitivity and reproducibility of ^{68}Ga PSMA PET/CT for the diagnosis and staging of patients with newly diagnosed PC have been noted as well (4). It is also been reported that SUV_{max}, which is the most widely used parameter for the quantification of radiotracer uptake of the tumor, may be used to differentiate malignant from benign lesions in the prostate gland, and correlation of SUV_{max} with PSMA expression is demonstrated (8,13). Increased ^{18}F-FDG uptake in primary cancers and eventually highly calculated SUV_{max} values showing proliferative activity of malignant tissue have also been reported in various tumors (14). Thus, the association of SUV_{max} with the biological aggressiveness of malignant tissue has been well established for both radiopharmaceuticals we used in our study.

To identify management strategies, it is crucial to answer the question of whether OM disease in PC is an indolent disease biology that the cancer is slow-growing and has limited metastatic potential or it is a result of existing metastatic disease, which is depicted with more sensitive imaging modalities an early time point (3). By Reyes and Pienta (15), the evolution of these two theories was summarized and it was underlined that the limited metastatic potential of OM disease could be attributable to less aggressive cancer clones that can metastases to few organs in contrast to MM disease, which harbors aggressive cancer clones able to metastases to multiple organs. Although could not be analyzed in our cases, by Uppal et al. (16), biological markers related to the OM phenotype with limited potential to develop multimetastasis were investigated, and three miRNAs named miR-127-5p, miR-544a, and miR-655-39, were shown to be associated with cells of low malignant potential in a model of breast carcinoma lung colonization. Studies assessing the clonality and metastatic potential between prostate cancer cells demonstrated that Ki67 expression and phosphatase and tensin homolog protein losses have been correlated with poor prognosis (17).

Results of quantification in primary tumors with extraprostatic metastases than those without metastases were compared and higher SUV_{max} in former ones were reported previously (4). In the study by Erdoğan et al. (18), the role of SUV_{max} of the primary tumor as a predictor of OM and MM disease in patients with PC was also demonstrated with ^{68}Ga PSMA. The unusual point of our study was investigating the results of SUV_{max} values in MM and OM disease and comparing the results between them for two different radiopharmaceuticals. Interestingly, SUV_{max} values calculated from metastatic lesions of PC patients were found to be significantly higher in MM compared with OM disease for both ^{18}F-FDG and ^{68}Ga PSMA. Since the accumulation of former radiopharmaceuticals shows glucose metabolism and uptake of later is associated with receptor expression level, statistical analysis for comparing SUV_{max} values was performed separately. In the area of PC, a fair amount of genetic heterogeneity both between patients and between different disease sites in a single patient is observed (7). Taking into consideration the relation of SUV_{max} with tumor proliferation rate and its biological behavior, we thought that this difference may be secondary to the different aggressiveness of metastatic cells in OM and MM patients, which may support the hypothesis suggesting their distinct biological origin. Prostatic radiopharmaceutical uptake, on the other hand, was not found to be significantly different between these two diseases, which may be attributed to the low number of patients in subgroups and was discordant with the results of Erdoğan et al. (18). Besides, the highest SUV_{max} result calculated from the prostate site (122.04) was observed in the OM group, which might play a role as an extreme value and affect the statistical analysis in our study. However, GS, which is a marker of aggressiveness and risk for disease recurrence in PC, was not associated with the type of metastatic disease. We thought that whether it is OM or MM, the disease is metastatic; it has gained metastatic potential employing leaving primary tumor and evading

the immune system in contrast to non-metastatic PC. Since all patients were metastatic in our study, we could not observe any difference in the frequency distributions of OM and MM patients in terms of GS.

Concordant with the results of Afshar-Oromieh et al. (2), we found that both in patients with OM and MM disease, bones were the most commonly involved metastatic areas than the other sites. In the OM group, PSMA positivity was limited to the pelvis in 68% of our patients, which was also a similar result with the literature (19). When we looked at the results of semi quantification of metastatic sites, we saw those lymph node metastases presented with the highest contrast in most cases and this was also concordant with the results reported before (2,4).

Study Limitations

Because of consisting of patients who had gone through therapy for primary disease, accumulation of radiopharmaceutical in the prostate gland was observed in a limited number of patients in our study, which can be mentioned as a limitation as well. Most patients with prostatic uptake were the ones with *de novo* disease in our study. In the ^{18}F-FDG group, 15 of 30 patients with *de novo* disease did not show radiotracer uptake in the prostate gland (Table 3), which may be secondary to the low glycolytic activity of the primary tumor. Absent radiopharmaceutical uptake of the prostate site was recognized only in 1 patient with *de novo* disease in the ^{68}Ga PSMA group, which can be attributed to a small tumor mass that does not express adequate tracer uptake (20). Another limitation of our study is being heterogeneous, having both *de novo* and post-therapy patients and eventually a low number of patients in subgroups, especially in the OM group. A low number of patients with OM disease may also be evolved secondarily to the criteria we used for the number of metastatic lesions for the definition of OM disease. If we took patients with more than 3 but less than five lesions in the OM group, we would have more patients with OM disease. Finally, GSs were not available in all patients and this was also a limitation of our study. Taken together, the limitations of our study were specific to its retrospective origin.

Conclusion

In conclusion, molecular imaging with PET/CT may play a role in identifying the biology of OM and MM disease in patients with PC. SUV_{max} results of metastatic lesions are significantly higher in patients with MM than in patients with OM disease for both ^{18}F-FDG and ^{68}Ga PSMA, which may be secondary to their different biological contents in terms of aggressiveness. Further studies with a larger number of presented *de novo* are needed to investigate whether prostatic uptake also differs or not between these two diseases, which may strengthen this hypothesis.

Ethics

Ethics Committee Approval: The study was approved by the Selcuk University Faculty of Medicine Ethics Committee (meeting date: 25.12.2019, decision number: 2019/382).

Informed Consent: Written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.Y., Concept: G.K.G., Design: G.K.G., Data Collection or Processing: G.K.G., Analysis or Interpretation: G.K.G., Literature Search: H.Ö., Writing: G.K.G.

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