Characterization of bone metastases detected on ^{68}Ga-PSMA PET/CT in newly diagnosed prostate cancer

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Abstract

Objective: This study sought to investigate the characteristics of bone metastasis (BM) and the association of BM with clinicopathological factors in prostate cancer (PCa) patients presenting with BM on the initial staging gallium-68-prostate-specific membrane antigen (^{68}Ga-PSMA) positron emission tomography/computed tomography (PET/CT). **Materials and Methods:** Patients with at least one BM in the initial staging ^{68}Ga-PSMA PET/CT between January 2018 and December 2021 were reviewed retrospectively. Types of BM were classified according to ^{68}Ga-PSMA PET/CT findings as osteoblastic (OB), osteolytic (OL), intramedullary (IM) and coexistence of these types. Patients were divided into two groups according to the number of BM: Oligo-BM for those with five or fewer BM and poly-BM for those with more than five BM. Receiver-operating characteristic (ROC) curves were generated for serum bone-specific alkaline phosphatase (ALP) and prostate-specific antigen (PSA) levels to discriminate between oligo-BM and poly-BM groups. Univariate and multivariate logistic regression tests were performed to find independent predictors of poly-BM. **Results:** A total of 53 patients with a median age of 70 (range: 49-88) were included in the study. The median Gleason score of the patients was 8 (range: 6-10). Among the patients, 23 had solely OB-type; 10 had solely IM type; 12 had OB and IM type; four had IM and OL type, two had OB and OL type; one had solely OL type, and one had IM and OB and OL type BM. Oligo-BM was detected in 25 patients (47.2%) and poly-BM was detected in 28 patients (52.8%). In multivariate analyses, serum ALP levels ≥122U/L and PSA levels ≥85.4ng/mL were found to be independent predictors of poly-BM. **Conclusion:** In characterizing BM of PCa, we found that OB-type metastases were the most common type, followed by IM-type and OL-type metastases, respectively. High ALP and PSA levels were found to be independent predictors of poly-BM.

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Introduction

Prostate cancer (PCa) is the second most common malignancy in men after lung cancer [1]. Metastasis of PCa is most commonly seen in the bones. Bone metastasis (BM) is seen in approximately 10% of newly diagnosed PCa patients, while this rate increases to 80%-90% in the course of the disease [2, 3]. Bone metastases are an important cause of morbidity in patients with PCa [4].

Bone scintigraphy is the most widely used imaging technique in the investigation of BM due to its low cost and high sensitivity [5]. In clinical and imaging guidelines, bone scintigraphy is recommended for the initial staging of intermediate and high-risk PCa [6, 7]. The uptake mechanism of technetium-99m-methylene diphosphonate (^{99m}Tc-MDP) radiopharmaceutical used in bone scintigraphy is closely related to the osteoblastic (OB) activity and increased blood flow of the lesion. However, the negative aspects of bone scintigraphy are the inability to detect small BM that does not cause an adequate osteoblastic response in the bone marrow and low specificity [8, 9]. Advances in imaging revealed that many different types of BM cannot be detected by bone scintigraphy in PCa, which is traditionally assumed to cause OB-type metastases. Prostate-specific membrane antigen (PSMA) is superior in detecting BM in PCa compared to positron emission tomography (PET) imaging using other agents (choline and fluoride), bone scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) [10]. Characteristics of BM in PCa have been a matter of interest following the widespread clinical use of this agent.

The extent of bone disease is one of the important prognostic factors in PCa and affects treatment management [11]. It has been reported that patients with five or fewer BM have longer overall survival than those with more BM [12]. Current evidence suggesting that patients with the oligometastatic disease may be candidates for curative therapy increases the importance of metastasis-directed therapies [5].

In the present study, we investigated the characteristics of BM in PCa patients presenting with BM in the initial staging gallium-68 (^{68}Ga)-PSMA PET/CT scan and the distribution of BM types according to the International Society of Urological Pathology (ISUP) grade groups [13]. We also evaluated the diagnostic performance of bone-specific serum marker alkaline phosphatase (ALP) and prostate-specific antigen (PSA) values in the discrimination of patients with high and low numbers of BM.

Materials and Methods

The study was approved by the Selçuk University, Faculty of Medicine, Research Ethics Committee, approval number 2022/70.

We analyzed the clinicopathological data of 864 patients who underwent ^{68}Ga-PSMA PET/CT in our department between January 2018 and December 2021. Of these patients, 53 patients with at least one BM who underwent ^{68}Ga-PSMA PET/CT for initial staging were included in the study. According to ^{68}Ga-PSMA PET/CT findings, the types of BM were grouped as osteoblastic (OB), osteolytic (OL), intramedullary (IM) and combinations of these types. In addition, the patients were divided into two groups according to the number of BM: Oligo-BM those with five or fewer BM, poly-BM those with more than five BM. Patients' age, Gleason score, ISUP grade, ALP, and PSA values were recorded. Patients were divided into two groups according to the ISUP grade as ≤3 and>3. The distribution of BM types in ISUP grade groups was also evaluated. The role of high ALP and PSA values in the discrimination between the oligo-BM and poly-BM groups was also investigated.

^{68}Ga-PSMAPET/CT imaging

The patients were imaged using a dedicated PET/CT system (Biograph mCT, Siemens, Erlangen, Germany). The patients were injected with 1.8-2.2MBq per kilogram/body weight of ^{68}Ga-PSMA. Hybrid image acquisition began 60 minutes after the ^{68}Ga-PSMA injection. The patients were instructed to void immediately before acquisition. Computed tomography scan (5-mm slice thickness) from the base of the skull to mid-tight (8-9 bed positions, 3 minutes per bed position) was acquired according to a standardized protocol (140kV and 80mA). The subsequent PET scan was acquired in a 3-dimensional mode from the base of the skull to mid-thigh. Anatomical co-registration and attenuation correction was performed using CT images.

Image analysis

Experienced nuclear medicine physicians evaluated ^{68}Ga-PSMA PET/CT images by consensus. The maximum standardized uptake value (SUVmax) of the primary prostate lesion was obtained by drawing the area of interest from the lesion using commercial software (Syngo. Via, Siemens Medical Solutions). Any bone lesion showing an uptake above physiological was recorded according to the PSMA-RADS, version 1.0 system [14]. Bone metastasis types were classified according to ^{68}Ga-PSMA PET/CT findings as follows; OB-type, focal increased ^{68}Ga-PSMA uptake corresponding to the lesion showing higher density than the surrounding bone tissue on CT; OL-type, focal increased ^{68}Ga-PSMA uptake corresponding to the lesion causing bone destruction; and IM-type, focal increased ^{68}Ga-PSMA uptake in intact bone on CT [15].

For practical and ethical reasons, the histopathological diagnosis was absent in most BM. Therefore, all current and follow-up laboratory findings and imaging studies (serum PSA measurements, bone scintigraphy, CT/MRI, and ^{68}Ga-PSMA PET/CT) were used with consensus to evaluate suspicious bone findings. Previous studies have also used this method [5, 16-18]. According to this method, which is defined as the best valuable comparator (BVC), lesions such as hemangioma, fracture and enostosis were not evaluated in the study. Suspicious lesions on ribs that did not show morphological changes on CT were considered as "non-specific bone uptake" as previously described [19, 20] and were not included in the study as BM. Morphologically typical or benign bone changes such as bone islands were not considered BM.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (IBM SPSS Statistics for Windows, v26, IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequency and percentage. Continuous variables were evaluated for the normality of distribution using histograms. Since the study variables were not normally distributed, continuous variables were expressed as medians and ranges. Mann-Whitney test was used to compare continuous variables between oligo-BM and poly-BM groups. To evaluate the diagnostic performance of serum ALP and PSA in distinguishing between oligo-BM and poly-BM groups, receiver operating characteristic (ROC) curves were generated and the Youden Index was used to calculate optimal cut-off values [9]. A multivariate logistic regression model was used to determine independent predictors for poly-BM using the parameters with a P-value <0.05 in univariate analyses. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. A value of P<0.05 was considered statistically significant.

Results

A total of 53 patients with a median age of 70 (range: 49-88) were included in the study. The median Gleason score of the patients was 8 (range: 6-10). The ISUP grade groups of the patients were distributed as follows: one patient (1.9%) with grade I, three patients (5.6%) with grade II, nine patients (17.0%) with grade III, 15 patients (28.3%) with grade IV, and 25 patients (47.2%) with grade V tumors. The demographic data of the patients are summarized in Table 1.

Among the patients, 23 had solely OB-type; 10 had solely IM type; 12 had OB and IM type; four had IM and OL type, two had OB and OL type; one had solely OL type, and one had IM and OB and OL type metastases. Representative images of different BM types are presented in Figure 1.

Oligo-BM were detected in 25 patients (47.2%) and poly-BM were detected in 28 patients (52.8%). No significant dif-

Table 1. *The demographic data of the patients.*

Median age (y) (range)	70 (49-88)
Median SUVmax of primary tumors	19.36 (4.27-105.07)
Median ALP (U/L)	117 (52-4839)
Median PSA (ng/ml)	120 (6.32-883)
Median Gleason score	8 (6-10)
ISUP groups	
I	1 (1.9%)
II	3 (5.6%)
III	9 (17.0%)
IV	15 (28.3%)
V	25 (47.2%)
Bone metastasis groups	
Oligometastatic disease	25 (47.2%)
Polymetastatic disease	28 (52.8%)

ALP, alkaline phosphatase; ISUP, International Society of Urological Pathology, PSA, prostate-specific antigen; SUVmax, maximum standardized uptake value.

ference was found between the SUVmax value of the primary prostate lesion in the oligo-BM and poly-BM groups (P=0.291). The median ALP (112U/L vs. 123.5U/L, respectively and P=0.001) and PSA values (38.7ng/mL vs. 150ng/mL respectively and P=0.006) of the poly-BM were significantly higher than the oligo-BM group. Cut-off values were 122U/L [AUC: 0.773 (0.58-0.835), P=0.002] for ALP and 85.4ng/mL [AUC: 0.721 (0.637-0.876), P<0.001] for PSA. With these cut-off values in distinguishing oligo-BM and poly-BM groups sensitivity of 53.6% and a specificity of 84% were found for ALP and a sensitivity of 75% and a specificity of 64% were found for PSA. In univariate and multivariate logistic regression analyses, serum ALP ≥122U/L (HR: 4.565 CI: 1.288-16.186, P=0.019) and PSA ≥85.4ng/mL (HR: 6.214, CI: 1.548-24.943, P=0.01) values were independent predictors of poly-BM. Table 2 shows the univariate and multivariate logistic regression analysis for the prediction of poly-BM.

Of 10 patients with PSA <20ng/mL; oligo-BM were observed in seven of them and poly-BM in three of them. While two patients (3.8%) with ISUP grade ≤3 had oligo-BM; 23 patients (43.9%) with ISUP grade >3 had oligo-BM. On the other hand, three patients (5.6%) with ISUP grade ≤3 had poly-BM; 25 patients (47.2%) with ISUP grade >3 had poly-BM. In Figure 2, the distribution of oligo-BM and poly-BM groups in ISUP grade groups is shown with a histogram table.

Osteoblastic-type metastases in the oligo-BM group were found in one patient with ISUP grade I. One IM and one OB single type metastasis were detected in two patients with ISUP grade II. Oligo-BM including IM and OB type metastasis was detected in one patient with ISUP grade II.

Discussion

The mechanisms underlying the observation of different types of BM in PCa are not yet fully understood. However, it has been reported that BM begins as intramedullary and reach

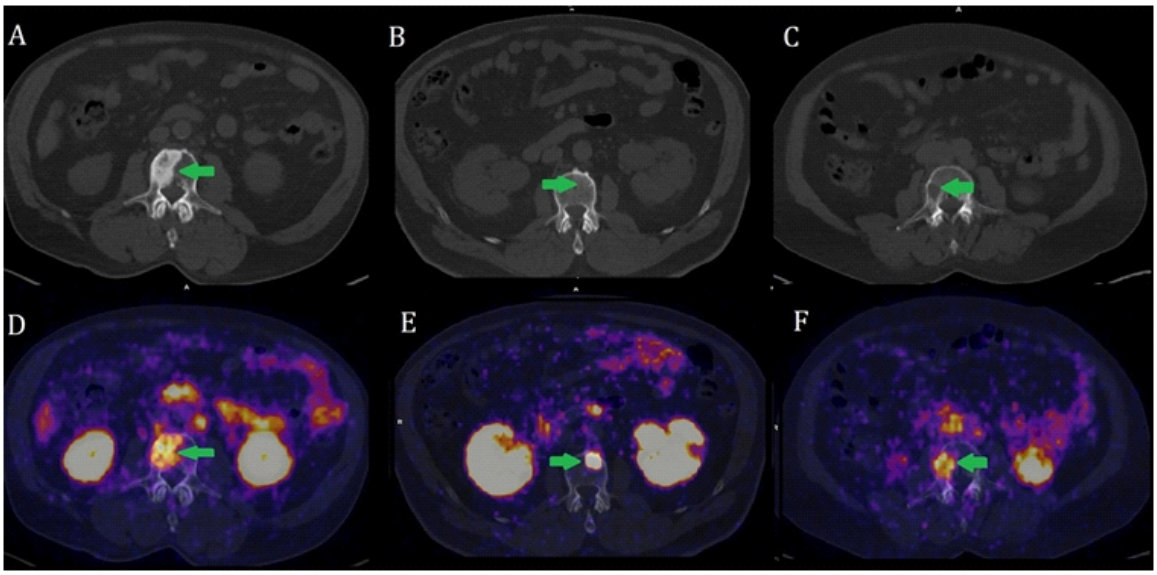

Figure 1. Representative images of different types of bone metastases (green arrow) on ^{68}Ga-PSMA PET/CT. A, D- osteoblastic metastasis; B, E- intramedullary metastasis; C, F- osteolytic metastasis. A, B, C- CT; D, E, F- fusion image. ^{68}Ga-PSMA PET/CT, ^{68}Ga-prostate-specific membrane antigen positron emission tomography/computed tomography.

Table 2. *Univariate and multivariate logistic regression analysis for prediction of multimetastatic form of bone metastasis in prostate cancer patients.*

	Univariate logistic regression analysis			Multivariate logistic regression analysis		
Variables	**HR**	**95% confidence interval**	**P value**	**HR**	**95% confidence interval**	**P value**
Primary tumour's SUVmax>19.36	1.697	0.572-5.037	0.341			
ISUP grade >3	2.165	0.601-7.795	0.237			
ALP ≥122U/L	6.058	1.648-22.269	0.007	4.565	1.288-16.186	0.019
PSA ≥85.4ng/mL	4.444	1.397-14.138	0.012	6.214	1.548-24.943	0.010

HR, Hazard ratio, SUVmax; Maximum standardized uptake value.

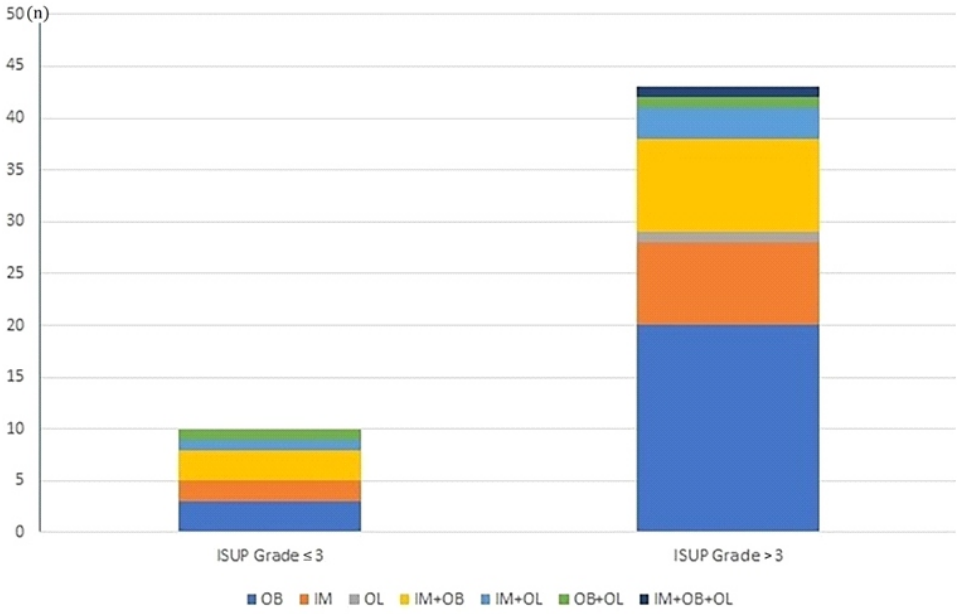

Figure 2. The distributions of bone metastases types in two ISUP grade groups. ISUP, International Society of Urological Pathology; OB, osteoblastic; IM, intramedullary; OL, osteolytic.

reach their final appearance after a series of molecular processes [21-24]. If the earliest detectable BM represents intramedullary metastases, it is not possible to detect BM with conventional methods such as bone scintigraphy and CT at this stage. In many malignancies, such as in PCa, undetected and untreated BM may lead to severe bone pain, spinal cord compression, pathological fracture and even death [25-27].

In recent years, a promising new tracer more specific to PCa cells has led to a significant change in the treatment management of PCa patients. Fluorine-18 or ^{68}Ga-PSMA is superior to bone scintigraphy and other radiological imaging methods in the detection of BM [10, 17]. With the widespread clinical use of PSMA PET, BM can be detected at an earlier stage. Moreover, in the ^{68}Ga-PSMA PET/CT fusion imaging modality, the superior ability of ^{68}Ga-PSMA PET to detect IM/OL-type metastases combined with the high sensitivity of CT to detect OB-type metastases produced a synergistic effect [15]. Specificity values for ^{68}Ga-PSMA PET have been reported to be 98.8%-100% in BM of PCa patients [17] and its high interobserver correlation for BM suggests that ^{68}Ga-PSMA PET/CT [28] has high reliability in this regard.

The BM of PCa is traditionally described as "OB type". Although OB is the predominant type of metastasis in PCa, recent studies have shown high heterogeneity in BM types, with the coexistence of OL and IM types [15, 29, 30]. In the present study, the rates of BM types were similar to that re-

ported in these previous studies. Osteolytic-type metastasis was seen only in one patient and it was together with other metastasis types in eight patients. Except for radionuclide palliative therapies targeting the bone, the type of BM usually does not influence the choice of systemic treatment options [27]. For radionuclide pain palliation treatments targeting the bone, the metastasis type should be OB-type. However, it is not yet known which type of BM is more responsive to PSMA-targeted radionuclide therapies, which have had promising results with the theranostic approach in PCa patients in recent years, so it needs to be investigated.

Clinical guidelines recommend bone scintigraphy for staging in patients with the following conditions: a PSA ≥20; clinical stage T2 and a PSA ≥10ng/dL; clinical stage T3 or T4; Gleason score ≥8 and any symptoms suggestive of BM [6, 31]. In our study population, OB-type metastasis was detected in one patient with ISUP grade I. Intramedullary and OB-type BM were detected in two patients with ISUP grade II. While solely IM and solely OB-type BM were detected in two patients with ISUP grade II, one patient with this ISUP grade had mixed IM and OB type oligo-BM. Of 10 patients with a PSA <20ng/mL, seven had oligo-BM and three had poly-BM. Similarly, in a recent study [30], it was reported that BM may also occur in patients with ISUP grade ≤2/3 and PSA <10ng/dL, but at a low incidence.

The extent of BM in PCa patients is one of the important prognostic factors affecting treatment management [11]. The dichotomization of PCa patients into oligo-BM and poly-BM groups according to the number of BM enables clinicians to assist in selecting more effective therapies [12]. In a recent study, radiotherapy was shown to be an effective and well-tolerated treatment option for PC patients with five or fewer bone-only oligometastases on ^{68}Ga-PSMA PET/CT [32]. The univariate and multivariate regression analyses in the present study revealed that ALP and PSA were independent predictors of poly-BM. Wymenga et al. (2001) reported that the increase in ALP levels is closely related to the increase in the extensiveness of the BM [33]. In another study, it was reported that the risk of BM is high in patients with PSA level>39.58ng/mL and ALP level >91.0U/L in addition to other clinicopathological factors [34].

The study's retrospective nature was one of the main limitations. Also, histopathological confirmation from all BM was technically and ethically not possible. Therefore, the BVC approach was used for evaluating suspicious bone lesions, as in similar studies [5, 16-18]. Since the ^{68}Ga-PSMA PET/CT study is not performed in our institution up to the toe, we could not evaluate the bone lesions between the mid-thigh and toe. Another limitation is the evaluation of patients in a single-center and the small sample size of the study. Large cohorts, prospective and multicenter studies are needed to confirm our findings.

In conclusion, in this study which investigated the characterization of BM of PCa, we found that IM and OL-types were present after OB-types, respectively. Another finding of the study is that BM can also be seen in the low-risk group (PSA <20, ISUP grade groups <3). ALP ≥122U/L and PSA ≥85.4 ng/mL were found to be independent predictors of poly-BM. Oligo-BM should be investigated for possible curative treatments in patients with ALP and PSA values below these values.

The authors declare that they have no conflicts of interest.

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