Correlations of ^{68}Ga-PSMA PET/CT in the initial staging of prostate cancer patients

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Abstract

Objective: The aim of this study was to evaluate the correlations between the different risk groups of prostate cancer (PCa) regarding the presence of metastasis and the gallium-68 prostate specific membrane antigen (^{68}Ga-PSMA) uptake patterns in the prostate gland. **Materials and Methods:** One hundred thirty nine patients with newly diagnosed, untreated PCa who underwent ^{68}Ga-PSMA PET/CT imaging for staging between July 2017 and March 2019 were enrolled in this retrospective study. Maximum standardized uptake values (SUVmax) were determined by manually placing the region of interest to the primary tumor in the prostate gland. Patients were divided into groups according to their prostate-specific antigen (PSA) values, International Society of Urological Pathology (ISUP) grade groups, Gleason Scores (GS), D'Amico risk stratification criteria and the presence of metastasis. Mann Whitney U test was used in the comparison of two groups of data. In multivariate analysis, logistic regression was used to determine independent predictors for the presence of metastasis. **Results:** There were statistically significant differences between D'Amico risk groups in terms of prostate SUVmax levels. The SUVmax levels of the patients in the high risk group were significantly higher than the SUVmax levels of the patients in the low-medium risk groups (P<0.001). Maximum standardized uptake value levels of the patients with PSA level 20ng/mL and above were significantly higher than those with PSA level below 20ng/mL (P<0.001). The metastatic rate of patients with ^{68}Ga-PSMA uptake on two lobes of the prostate gland was significantly higher (42.6%) than the metastatic rate of patients with ^{68}Ga-PSMA uptake on only one lobe (7.9%) (P<0.001).The median SUVmax of tumours in patients with metastasis was statistically significantly higher than in patients with no metastasis. In multivariate analysis; bilobar involvement, PSA value 20ng/mL, prostate SUVmax value 8.6 and GS 8 were determined as independent predictors for the presence of metastasis. **Conclusion:** The strong correlation between PSA values and/or Gleason score/Grade and SUVmax values suggests that the SUVmax value of the prostate gland might be a valuable determinant in risk classifications.

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Introduction

Prostate cancer (PCa) is the most common cancer and the second leading cause of cancer death among men in the western world [1]. Patients with prostate cancer are considered as low, medium or high risk of progression according to clinical stage, Gleason score (GS) and serum prostate specific antigen (PSA) level as per the International Society of Urological Pathology guidelines (ISUP)[2]. Prostate specific membrane antigen (PSMA), which is overexpressed (over 100- to 1000- fold) in PCa cells, is a type II transmembrane glycoprotein. Increased expression of PSMA is correlated with higher GS and the development of metastatic disease [3]. Prostate specific membrane antigen expression is not specific to PCa and elevated uptake of PSMA-ligands has been observed with various neoplasms, malignancies and even in the case of inflammation or infection. Gallium-68-PSMA is one of the recently developed positron emission tomography (PET) radiotracers that binds to PSMA [4].

Several studies have been performed to prove that ^{68}Ga-PSMA PET/CT is a highly accurate technique for detecting PCa metastases and relapses but data on the use of ^{68}Ga-PSMA PET/CT as an initial staging modality is limited [5]. Although the use of ^{68}Ga-PSMA PET for primary staging of PCa is promising, it remains limited because of the absence of high quality evidence to support its use [6].

The aim of our study is to evaluate the correlations between the different risk groups of PCa regarding the presence of metastasisand PSMA uptake pattern/SUVmax values of the primary lesion.

Materials and Methods

The files of PCa patients who were referred to our clinic for ^{68}Ga-PSMA PET/CT imaging between July 2017 and March 2019 were examined retrospectively. Out of 380 patients, 139 patients (mean age: 70±8 years, range: 50-90 years) who applied for primary staging with histopathologically proven PCa (including a GS), and without any prior PCa treatment were included in the study. Two hundred forty one patients without pathological confirmation of PCa and with a history of prior medical or surgical treatments for PCa were excluded from the study.

For each patient, the patient characteristics including age, disease stage, GS, PSA values were obtained at the time of the scan. Patients were categorized into three different risk groups (low-, medium-, and high-risk groups) according to the D'Amico risk stratification criteria taking clinical primary tumour stage, serum PSA levels, and GS into account [7]. Gleason Grade (GG) groups were formed according to the Gleason Gradingsystem suggested by ISUP in 2014. With regard to D'Amico criteria, the highest value among the variables was considered for risk stratification purposes (Low risk group (PSA<10ng/mL and GS <7 and T1-T2a), intermediate risk group (PSA 10-20ng/mL or GS 7 or T2b-T2c) and high risk group (PSA >20ng/mL or GS 8-10 or T3-T4). Gleason score and PSA criteria defining patients who would benefit from ^{68}Ga-PSMA PET/CT imaging for staging was determined.

Radiolabelling of ^{68}Ga-PSMA Imaging and image acquisition

Preparation of PSMA-targeting ligand ^{68}Ga-PSMA I&T was synthesized by a fully-automated, good manufacturing practice–compliant procedure using a GRP module (SCINTOMICS GmbH, Germany) connected to a ^{68}Ge/^{68}Ga generator (iThemba. Labs, S.A) and equipped with a disposable single-use cassette kit (ABX, Radeberg, Germany).

The radiochemical purity of ^{68}Ga-labeled PSMA conjugates was ≥95%. After the preparation and quality control of the radiotracer, all patients received 65 to 178MBq (mean 113.3±21.2MBq) of ^{68}Ga-PSMA according to the yield of the radiolabeling. Imaging was performed approximately 60 minutes after radiotracer intravenous injection. The patients were well hydrated and voided immediately before the scan. Whole body PET/CT imaging was performed on a biograph (Siemens Biograph 6, Chicago, IL, USA) using a full-ring HI-REZ LSO PET and a six-slice CT scanner. Firstly, non-enhanced CT scan was performed with the following parameters: 40-60mAs, 140kV and 5-mm section thickness. Positron emission tomography emission scanning with 3min per bed position was then acquired on the identical transverse field of view in the caudocranial direction. Computed tomography transmission images were used for attenuation correction, and images were reconstructed using an iterative method.

Image analysis

Maximum standardized uptake value was determined by manually placing a region of interest (ROI) using the ellipsoid isocontour on the primary tumor as well as the most prominent lymph nodes (LN), bone and soft tissue lesions. Lesions were considered positive if they exhibited PSMA uptake above background, not attributable to physiologic distribution. The findings were classified as; primary tumour, LN metastasis, bone metastasis and visceral organ metastasis. In addition, focal PSMA uptake in the prostate gland was divided into two groups depending on whether a single or both lobes were involved.

Ethical approval

Our study was approved by the local ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A written informed consent form was taken from each of the patients before undergoing ^{68}Ga-PSMA PET/CT imaging and all participants were assured about the study.

Statistical analysis

Statistical analysis was done using the statistical software NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) programme. In the evaluation of the study data, descriptive statistical methods (mean, standard deviation, median, minimum, maximum) were applied. Kolmogorov-Smirnov and Shapiro Wilks tests were performed to assess normality of all variables. Two groups of data were compared by Mann Whitney U test and Kruskal Wallis test was used in the comparison of three or more groups. Chi-Square test was used to compare qualitative data. The correlation among GS, SUVmax and PSA values in all patients were evaluated by Spearman correlation analysis. The statistical significance level was set at a P value of <0.05. The power of SUVmax in distinguishing the presence of metastasis was assessed by receiver operating curve (ROC) analysis; in this analysis, area under curve (AUC), cut-off value according to Youden index were calculated. Subsequently, sensitivity and specificity values were determined at this cut-off value. In multivariate analysis, logistic regression was used to determine independent predictors for the presence of metastasis.

Results

A total of 139 patients prior to particular treatment for PCa were enrolled in the study. The patients' data are summarized in Table 1.

The median PSA level was 15.44ng/mL (0.45-2048.00). Forty-three (30.9%) patients had PSA values less than 10ng/mL, 40 (28.8%) had PSA values of 10-20ng/mL and 56 (40.3%) had PSA values greater than 20ng/mL.

Histopathology was adenocarcinoma in all patients with a GS of 6 in eleven patients (7.9%), 7 in sixty-four patients (46%), 8 in forty-five patients (32.4%), 9 in seventeen patients (12.2%) and 10 in two patients (1.4%). Based on the D'Amico risk stratification system, the majority of patients (n:91) included in this study had high-risk prostate cancer (65.5%). Three patients were in the low-risk group and 45 patients (32.4%) were in the intermediate-risk group.

All of the patients had ^{68}Ga-PSMA uptake in their prostate gland. Thirty-eight patients (27.3%) had ^{68}Ga-PSMA uptake in one lobe of the prostate gland, while the remaining 101 pati-

Table 1. Distribution of Descriptive Properties.

Age	**Mean±SD (range)**	**70±8 (50-90)**	
Serum PSA (μg/L)	Median (Min-Max)	15.4 (0.5-2048.0)	
	PSA <10ng/mL	43	30.9%
	PSA 10-20ng/mL	40	28.8%
	PSA ≥20ng/mL	56	40.3%
Lobes	Right lobe	20	14.4%
	Left lobe	18	12.9%
	Bilateral	101	72.7%
Grade Group	Grade 1	11	7.9%
	Grade 2	40	28.8%
	Grade 3	24	17.3%
	Grade 4	45	32.4%
	Grade 5	19	13.7%
Gleason Score			
	Score 6	11	7.9%
	Score 7	64	46.1%
	Score 8	45	32.4%
	Score 9	17	12.2%
	Score 10	2	1.4%
Gleason Score Groups	Score 6/7	75	54.0%
	Score 8	45	32.4%
	Score 9/10	19	13.6%
D'amico risk	Low risk	3	2.1%
	Medium risk	45	32.4%
	High risk	91	65.5%
Prostate SUVmax	Median (Min-Max)	9.2 (2.2-47.0)	
Lymph node SUVmax	Median (Min-Max)	17.3 (0-55.7)	
Bone lesion SUVmax	Median (Min-Max)	23.2 (3.0-47.6)	
Perineural invasion	No	64	46.0%
	Yes	75	54.0%
Metastatic/ Non metastatic	Non metastatic	93	66.9%
	Metastatic	46	33.1%

ents had ^{68}Ga-PSMA uptake in both lobes of the prostate gland.

Metastatic PCa was shown by ^{68}Ga-PSMA PET/CT imaging in 46 of the 139 (33.1%) patients. Nodal involvements were observed in 42 (91.3%) of the 46 patients with metastatic disease, whereas skeletal metastases were shown in 24 (52.1%) patients. All patients with skeletal metastases also had lymph node metastases. And six patients (13.4) had visceral organ metastases.

Median SUVmax in all patients' prostate glands was 9.2 (range2.2-47.0), median SUVmax for PSMA-avid lymph nodes was 17.3 (range: 1.6-55.7) and median SUVmax of bone lesions was 23.3 (range:3.0-47.6).

There was a statistically significant difference between PSA groups in terms of prostate SUVmax values (P=0.001). Maximum SUV levels of the patients with PSA level 20ng/mL and above were significantly higher than those with PSA level below 20ng/mL (P<0.001) (Table 2).

There were statistically significant differences among D'Amico risk groups in terms of prostate SUVmax levels. The SUVmax levels of the patients in the high risk group were significantly higher than the SUVmax levels of the patients in the low-medium risk groups (P<0.001) (Table 2).

Maximum SUV values of the patients in GG group 4 and above were found to be higher in comparison with those of the other patients in GG group below 4 (P=0.020) (Table 2).

The median SUVmax of primary tumours in patients with metastasis (n: 46) was statistically significantly higher than in patients with no metastasis (P<0.001, AUC:0.773, 0.697-0.849, 95%CI). When SUVmax cut-off value was determined as 8.6, sensitivity and specificity values in detecting metastasis were calculated as 87.0% and 60.2%, respectively. In the high-risk patient group, SUVmax values of the patients with and without metastasis differed from each other (P= 0.002).

When the GS groups were evaluated in terms of metastatic rates, the patients with GS 8 and above (46.9%) showed higher metastatic rate than those with GS 6/7 (21.3%) (P= 0.001) (Table 3).

When comparing metastatic rates of the PSA level groups, it was observed that the patients with PSA level 20ng/mL and above (64.3%) had higher rates than those with PSA level below 20ng/mL(12.0%) (P<0.001)(Table 3).

The metastatic rate of patients with PSMA uptake on two lobes of the prostate gland was significantly higher (42.6%)

Table 2. *The correlation of SUVmax with PSA, risk groups, presence of metastasis and GS.*

		n	Min-Max (Median)	P value
Serum PSA (μg/L)	PSA <20	83	2.2-47.0 (5.9)	<0.001*
	PSA ≥20	56	6.0-45.9 (15.8)	
Lobes uptake	Unilobar	38	2.2-47.0 (8.3)	0.146
	Bilobar	101	2.3-45.9 (10.0)	
Grade Groups	Grade ≥4	75	2.2-47.0 (8.0)	0.020
	Grade <4	64	3.1-40.8 (11.4)	
D'amico risk	Low-medium risk	48	2.2-47.0 (5.4)	<0.001*
	High risk	91	3.1-45.9 (12.7)	
Perineural invasion	Non	64	2.2-45.9 (8.9)	0.235
	Yes	75	3.1-47.0 (10.0)	
Metastatic /nonmetastatic	Nonmetastatic	93	2.2-47.0 (6.9)	<0.001*
	Metastatic	46	5.1-45.9 (15.8)	

**P<0.05, Mann Whitney U test*

Table 3. *Evaluation of parameters according to the presence of metastasis.*

		Non metastatic	Metastatic	
		n (%)	n (%)	P value
Serum PSA (μg/L)	PSA <20	73 (88.0)	10 (12.0)	<0.001*
	PSA ≥20	20 (35.7)	36 (64.3)	
Lobes	Unilobar	35 (92.1)	3 (7.9)	<0.001*
	Bilobar	58 (57.4)	43 (42.6)	
Gleason Score	Score 6/7	59 (78.7)	16 (21.3)	0.001*
	Score ≥8	34 (53.1)	30 (46.9)	
Local invasion	No	92 (71.3)	37 (28.7)	<0.001*
	Yes	1 (10.0)	9 (90.0)	
SUVmax	<8.6	56 (90.3)	6 (9.7)	<0.001*
	≥8.6	37 (48.1)	40 (51.9)	

**P<0.05*

than the metastatic rate of patients with PSMA uptake on one lobe (7.9%) (P<0.001) (Table 3). Prostate SUVmax measurements did not differ statistically with respect to lobe sides.

There were 10 (7.2%) patients with local invasion findings, while 90% of these patients had distant metastases: This rate was 28.7% in patients without local invasion and there was a significant difference between the groups with local invasion and without (P< 0.001).

When the correlation among unilobar/bilobar involvement, GS, PSA value, prostate SUVmax, presence of local invasion and metastasis were evaluated with multivariate analysis; bilobar involvement (P=0.027, HR:4.921, 1.204-20.113, 95% CI), PSA value of 20ng/mL and above (P=0.002, HR:4.858, 1.791-13.173, 95% CI), prostate SUVmax value of 8.6 and above (P=0.002, HR:5.879, 1.927-17.934, 95% CI) and GS of 8 and above (P=0.027, HR:2.857, 1.125-7.256, 95% CI) were determined as independent predictors for the presence of metastasis.

There was a moderate correlation between the SUVmax values and PSA (ρ=0.566, P<0.001). In addition, SUVmax values showed a weak correlation with grade groups based on biopsy reports (ρ=0.217, P=0.010).

Discussion

In the multivariate analysis performed in our study, the correlation between bilobar PSMA uptake in the prostate gland and the presence of metastasis was shown. Moreover, the rate of metastasis was found to be higher in patients with a GS of 8 and above, and patients with a PSA value of 20ng/mL and above. Maximum SUV values were significantly higher in patients with metastasis and in patients with high risk according to D'Amico risk grouping. These results show that PSMA overexpression of the primary prostate cancer may be a risk factor for prostate cancer recurrence and metastasis. Gallium-68-PSMA PET/CT imaging has a great potential in assessing the risk stratification and existence of metastasis of prostate cancer. Nkengurutse et al. (2020) wanted to determine predictors affecting biochemical recurrence after radical prostatectomy in 101 patients. In this study GS (<8 vs. ≥8; HR: 2.439) and clinical stage (≤cT2c vs. >cT2c; HR:3.271) were determined as independent predictors with Cox regression analysis [8]. In our study, it was shown that bilobar ^{68}Ga-PSMA uptake in the prostate gland, GS 8 and above are associated with the presence of metastasis.

The correlation between the intensity of ^{68}Ga-PSMA accumulation in the primary tumor and the patient's GS and PSA level has been studied, however, these studies in the literature have come to different conclusions. Fendler et al. (2016) reported that SUVmax of the entire prostate gland was significantly associated with PSA level but not GS [9]. Similarly, in Kuten et al. (2019) study, while there was a positive correlation between prostate gland SUVmax and PSA, there were no significant correlations among prostate gland SUVmax and GS or the presence of metastatic disease [10]. In our study, prostate SUVmax values were significantly correlated with both pretreatment PSA values and GG groups. In primary staging of PC, Sachkepides et al. (2016) found a statistically significant correlation between PSA values and SUVmax of primary tumours [11]. Albert El Haji's (2019) results revealed that SUVmax of the index lesions, which was the highest in the entire prostate, significantly correlated with the GS of the surgical specimen [12]. Bravaccini et al. (2018) found that PSMA expression on histological examination has been proportional to SUVmax value, GS, and PSA level [13]. Liu et al. (2018) reported that SUVmax values obtained from ^{68}Ga-PSMA-617 PET/CT correlated with GS and PSA value. In addition, there are other studies in the literature showing correlation between prostate SUVmax and PSA [14]. Demirci et al. (2019) found that the mean SUVmax values of high-risk patients according to the final pathology reports were notably higher than those of low-risk patients (P<0.001) [15]. Similarly, in our study, SUVmax values in high-risk patients were found to be significantly higher than in the low-medium risk group (P<0.001). There was a significant difference in SUVmax values between patients regardless of the existence of the metastasis in the high-risk patient group (P=0.001).

In patients with GS 4+3 and above, SUVmax values were found to be significantly higher than those with GS 3+3 and 3+4, and this is consistent with the information in the literature. In their study conducted with 90 patients with prostate cancer, Uprimny et al. (2017) found that the SUVmax values measured from the prostate glands of patients with a GS of 7 and below and those with a GS above 7 differ significantly [16]. In Ergül et al. (2018) study, a profound discrepancy was observed between GSs of 6 and 7 compared with GSs of 8, 9, and 10 (P=0.003) [17].

When patients with GS 7 were evaluated as GG 2 and 3, there was no significant difference between the GS 3+4 ratio in the medium-risk group and the GS 3+4 ratio in the high-risk group (P=0.741). Moreover, there was no remarkable difference in SUVmax values between GG2 and GG3 in our study. Similarly, SUVmax values between GG2 and GG3 in the study of Ergül et al. (2018) were insignificant [17]. Likewise, Uprimny et al. (2017) could not detect any significant difference in prostate gland PSMA uptake value in patients with GS3+4 and 4+3 (P=1.00) [16].

In the study of Uprimny et al. (2017), a significant difference was found between patients with a PSA value of 10ng/mL or less and patients with a PSA value above 10ng/mL in terms of prostate SUVmax values. In our study, when the PSA cut-off level was determined as both 10ng/mL and 20ng/mL, a significant difference was obtained in SUVmax values between the two groups, as patients with higher PSA levels exhibited remarkable higher tracer uptake in the primary lesion statistically

There are some limitations of this study. One of them is its retrospective nature. Secondly, histopathological correlation was not technically and ethically possible from all foci that were considered metastasis. But all metastatic patients were scanned with radiological imaging modalities at the same time of ^{68}Ga-PSMA PET/CT imaging in order to corroborate the metastatic foci. Furthermore, in our patient group, nonparametric tests were used for statistical analysis since non-normal distribution was observed. This was also one of the limitations of our work.

In conclusion, SUVmax values correlate significantly with the GG of the primary tumor and PSA values prior to treatment. Bilobar PSMA involvement in the prostate gland, GS of 8 and above, PSA value of 20ng/mL and above were determined as independent predictors for metastasis. In newly diagnosed patients, PSA value and/or GS alone can change the patient's risk group according to D'Amico risk classification. The strong correlation between PSA values and/or Gleason score/Grade and SUVmax values suggests that the SUVmax value of the prostate gland might be a valuable determinant in risk classification and could change the risk group.

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