Correlations of the ^{68}Ga-PSMA PET/CT derived primary prostate tumor PSMA expression parameters and metastatic patterns in patients with Gleason Score >7 prostate cancer

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Keywords: ^{68}Ga-PSMA PET/CT - PSMA expression parameters - Metastasis

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Received:
16 March 2020
Accepted revised:
3 July 2020

Abstract

Objectives: We aimed to investigate the correlations between the prostate specific membrane antigen (PSMA) expression parameters of the primary prostate tumor on gallium-68 (^{68}Ga)-PSMA positron emission tomography/computed tomography (PET/CT) with metastatic patterns in patients with Gleason Score (GS) >7 prostate cancer (Pca). **Materials and Methods:** This study included 55 PCa patients who had ^{68}Ga-PSMA PET/CT performed for staging. According to metastatic pattern, patients were divided into 3 groups as non-metastatic (N0M0), those with isolated pelvic lymph node metastasis (N1M0) and with distant metastasis (M1). The correlations between the primary tumor PSMA expression parameters such as maximum standardize uptake value (SUVmax), SUVmean, PSMA-TV (PSMA receptor expressing tumour volume), and TL-PSMA (total lesion PSMA receptor expression) on ^{68}Ga-PSMA PET/CT imaging and metastatic patterns were investigated. **Results:** There were 21, 9 and 25 patients in the N0M0, N1M0 and M1 groups, respectively. The PSMA-TV and TL-PSMA values were significantly higher in the N1M0 and the M1 patient groups compared to the N0M0 group, but there was no significant difference between the N1M0 and M1 groups. The primary tumor SUVmax and SUVmean values were not significantly different between the three groups. The optimal PSMA-TV cut-off value for metastasis was >8.07cm^3 (AUC 0.86) with sensitivity of 76.5% and specificity 85.7%. The optimal TL-PSMA cut-off value for metastasis was >93 (AUC 0.74) with sensitivity of 64%, and specificity 100%. **Conclusion:** The PSMA-TV and TL-PSMA values are strong markers for metastasis prediction in patients with GS >7 PCa but no other PSMA expression parameters can distinguish between N1M0 and M1 groups.

Hell J Nucl Med 2020; 23(2): 120-124 *Epub ahead of print: 27 July 2020* *Published online: 24 August 2020*

Introduction

Prostate specific membrane antigen (PSMA) is a type II transmembrane protein with glutamate carboxypeptidase/folate hydrolase activity. The expression of PSMA in normal or hyperplastic prostatic tissues is low, while it is high in prostate adenocarcinoma (PCa). High PSMA uptake in primary PCa ensures easy differentiation of the margins with low-uptake normal prostate tissue [1-3].

Gallium-68 (^{68}Ga)-PSMA positron emission tomography/computed tomography (PET/CT) imaging is an effective method for metastasis screening of high-risk PCa patients in the early stages and is increasingly used to ensure treatment planning is performed accurately [4, 5].

There are many studies performed to evaluate the correlation between metabolic parameters of the primary tumor on fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging (such as metabolic tumor volume (MTV), total lesion glycolysis (TLG), maximum standardized uptake value (SUVmax), SUVmean with metastasis prediction, clinical behavior, pathological data, prognosis determination, and treatment response [6-8]. However, there are very few studies performed about PSMA expression parameters of PCa on ^{68}Ga-PSMA PET/CT. Prostate specific membrane antigen-tumor volume (PSMA-TV) and total lesion-PSMA (TL-PSMA) were firstly described by Schmuck et al. (2017) in the literature [9]. They examined these volumetric parameters in patient groups with radical prostatectomy operation and biochemical recurrence present. In recent years, whole-body PSMA-TV and TL-PSMA values have begun to be used for treatment response evaluation in patients with metastatic PCa [10, 11].

In our study, we aimed to investigate the correlations between PSMA expression parameters (SUVmax, SUVmean, PSMA-TV and TL-PSMA) of the primary prostate tumor and

metastatic patterns in patients with Gleason Score (GS) >7 PCa who underwent ^{68}Ga-PSMA PET/CT imaging for staging.

Materials and Methods

Patients

This retrospective study included 55 PCa patients who had ^{68}Ga-PSMA PET/CT performed for staging between August 2017-December 2018. The mean age of patients was 67 years (range, 46-85 years). The following criteria were defined for patient selection:

- Primary PCa diagnosed with transurethral ultrasound-guided (TRUS) biopsy and GS >7.
- Have not undergone any treatment for PCa before ^{68}Ga-PSMA PET/CT imaging and had no secondary malignancy.

According to metastatic patterns, patients were divided into 3 groups as non-metastatic (N0M0), those with isolated pelvic lymph node metastasis (N1M0) and those with distant metastasis (M1). Serum PSA values were measured within 1 week before imaging.

Ethics committee approval was obtained with decision number 48670771-514.10 dated 01.22.2019 for this clinical study which was designed retrospectively.

Radiolabelling

A fully automated Scintomics GRP synthesis module with Scintomics Control Center and GRP-Interface software was used for the radiolabelling of ^{68}Ga-DOTAGA-PSMA (called ^{68}Ga-PSMA I&T). The ^{68}Ge/^{68}Ga generator was purchased from iThemba LABS, South Africa. DOTAGA-PSMA was purchased from Scintomics GRP, Germany via a local distributor. The synthesis of the ^{68}Ga peptides was performed using a cationic purification method with 20μg of peptide used for the reaction. The labelling efficiency and radiochemical purity were determined using radio thin-layer chromatography and radio-high-performance liquid chromatography. The radiochemical purities of ^{68}Ga-labeled PSMA conjugates were ≥95%.

Imaging

Patients were imaged using an integrated PET/CT scanner that consisted of a full-ring HI-REZ LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL, USA). All patients received oral contrast agent starting about six hours before imaging. Each patient was injected with a standardized weight-based dose of 2MBq/kg (range 70-180MBq). Diuretic (10mg furosemide) was injected intravenously just before the ^{68}Ga-PSMA I&T injection. At 60min post-injection, a whole-body PET/CT scan was conducted with an emission time of 3min per bed position. Before emission images, a non-contrast enhanced low-dose CT was performed for attenuation correction and anatomic localization with the following parameters: 50mA, 140kV, and 5mm section thickness. All patients were positioned feet first, supine on the scanning pallet with imaging from the upper thigh to the vertex with arms up.

Images analysis

The foci of uptake in the prostate gland were identified as representing a primary tumour if the accumulation of ^{68}Ga-PSMA was increased relative to comparable surrounding prostate tissue and PCa was proven by TRUS biopsy in this localization. Increased ^{68}Ga-PSMA uptake compared to background activity, which was located outside the prostate gland and not related with physiological activity regions, was considered positive for metastasis. The SUVmax, SUVmean, and primary prostatic tumour PSMA-TV (cm^3) were produced automatically from the volume of interest (VOI) by the workstation (Esoft) for each primary prostatic tumor. We used PET images to automatically generate the contours using a threshold-based segmentation method. In the literature, threshold values between 40% and 45% were used to calculate PSMA-TV, including volumetric analysis with ^{68}Ga-PSMA PET/CT. Standardized uptake value mean and TL-PSMA [9-12]. In our study, voxels greater than a threshold of 41% of SUVmax in the VOI were defined to measure PSMA-TV and SUVmean. Primary tumor TL-PSMA was calculated by MTV multiplied by the SUVmean.

Statistical analysis

When analysing the data obtained in the study, the IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analyses. When evaluating the study data, normal distribution of parameters was assessed with the Shapiro Wilks test. When assessing the study data, descriptive statistical methods (mean, standard deviation, frequency) were used in addition to the Kruskal Wallis test for comparison of parameters without normal distribution between groups and the Mann Whitney U test to identify the group causing the difference. Two-group comparisons of parameters without normal distribution used the Mann Whitney U test. For investigation of the correlations between parameters not abiding by normal distribution, Spearman's rho correlation analysis was used. The most appropriate cut-off point was chosen based on ROC curve analysis. Significance was analysed at $P< 0.05$ level.

Results

There were 21 (38.18%), 9 (16.36%) and 25 (45.46%) patients in the N0M0, N1M0 and M1 groups, respectively. Patient characteristics are given in Table 1. Mean primary tumor SUVmax, primary tumor SUVmean, primary tumour PSMA-TV and primary tumour TL-PSMA values are given in Table 2.

All patients included in the study had PSMA positive primary prostate lesions. Prostate specific membrane antigen-TV and TL-PSMA values in the N1M0 and M1 groups were found to be high at a significant level compared to the N0M0 group (P=0.000, P=0.002, respectively). Between the N1M0 and M1 groups, there were no statistically significant differences in terms of PSMA-TV and TL-PSMA values. The primary tumor SUVmax and SUVmean values were not different significantly between the three patient groups.

The optimal PSMA-TV cut-off value for metastasis determined from receiver operating characteristic (ROC) analysis

was >8.07cm^3 (AUC 0.86; 95% CI 0.763-0.957; P=0.000) with sensitivity of 76.5% and specificity 85.7%. The optimal TL-PSMA cut-off value for metastasis determined from ROC analysis was >93 (area under the curve (AUC) 0.74; 95% CI 0.579-0.901; P=0.028) with sensitivity of 64% and specificity 100%. The optimal serum PSA cut-off value for metastasis determined from ROC analysis was >34.62ng/mL (AUC 0.716; 95% CI 0.58-0.851; P=0.008) with sensitivity of 55.9% and specificity 90.5%.

Table 1. *Patient characteristics.*

Total patient (n)	55
Gleason score	
8	38
9	14
10	3
Serum PSA value	
>20 ng/mL	35
< 20 ng/mL	20
Metastatic Patern	
***Non-metastatic**	21
***Metastatic**	34
-Isolated pelvic lymph node metastasis	9
-Extrapelvic or distant metastasis	25
Bone metastasis	24
Extrapelvic lymph node metastasis	11
Organ metastasis	40

The mean serum PSA values was 21.41ng/mL (range, 5.49-69.12) in N0M0 group, 37.98ng/mL (range, 9.26-74.48) in N1 M0 group and 315.38ng/mL (range, 1.62-2048.83) in M1 group patients. The mean serum PSA value was positively correlated with PSMA-TV (P=0.003) and TL-PSMA (P=0.004), but there were no statistically significant correlations found between the serum PSA value with primary tumor SUVmax (P= 0.136) and SUVmean (P=0.197) parameters. The mean serum PSA values were significantly higher in M1 group (P=0.02) and N1M0 group (P=0.028) than N0M0 group but there was no statistically difference between M1 and N1M0 groups (P= 0.56). Of the 20 patients with serum PSA value <20ng/mL, 9 had metastasis. Of the metastasis patients, 7 had PSMA-TV values above the threshold value (Figure 1). Within this patient group, no patient with PSMA-TV value <4.6cm^3 was identified to have metastasis. Metastasis was present in 25 patients with serum PSA value >20ng/mL. Nineteen patients with metastasis had PSMA-TV value above the threshold value, while 20 patients had TL-PSMA value above the threshold value. Of 10 patients with serum PSA value >20ng/mL and no metastasis, 9 had PSMA-TV values below the threshold. Within this patient group, no patient with PSMA-TV value <3.37cm^3 had metastasis identified (Figure 2).

Discussion

In PCa patients, ^{68}Ga-PSMA PET/CT imaging can provide identification of primary prostate gland tumor and delineation of intraprostatic spread with high accuracy. A study by Zamboglou et al. (2016) of 9 PCa patients compared 3-dimensional (voxel-wise) registration of ^{68}Ga-PSMA PET/CT imaging findings with prostatectomy pathology and concluded that lesion identification and delineation of margins was accurately performed for 8 patients [13]. Berger et al. (2018) showed that PSMA PET/CT can be reliably used to identify the prostatic index carcinoma with 100% detection rate, 81.1% sensitivity and 84.6% specificity [14].

Upriminy et al. (2017) found that the primary tumor ^{68}Ga-PSMA uptake of patients with GS >7 was significantly higher than those with GS ≤7 [15]. This was our reason for limiting the patient group to only GS >7 patients. All patients included in our study had PSMA positive primary prostate lesions. Schmuck et al. (2017) examined PSMA derived volumetric parameters in patients with biochemical recurrence after radical prostatectomy and concluded that PSMA-TV and TL-PSMA can better assess the tumor burdens of metastatic lesions than SUVmax, which had a better correlation with the patients' PSA levels. At the same time, they identified that treatment response and treatment failure were paralleled by concordant changes in both whole-body PSMA-TV and whole-body TL-PSMA [9].

Liu et al. (2018) were the first group to study PSMA expression parameters of the primary tumor on ^{68}Ga-PSMA-617 PET/CT imaging and the association with risk group and metastasis prediction. They included 40 PCa patients (27 with GS >7) with GS from 6-10 in the low-moderate-high risk groups in their study. They identified metastasis in 15 of the patients included in the study (38%). They found that SUVmax, PSMA-TV, and TL-PSMA could all effectively predict high-risk prostate cancer and PSMA-TV and TL-PSMA could predict the metastatic risk of PCa [16]. In our study, the PSMA-TV and TL-PSMA values in the N1M0 and M1 groups were significantly high compared to the N0M0 group. Different from Liu et al. (2018), we tried to find if there is a statistically significant difference between the N1M0 and M1 groups in terms of PSMA-TV and TL-PSMA values. We did not find a statistically significant difference between the N1M0 and M1 groups.

There are some studies in the literature reporting that the degree of PSMA expression and consequently SUVmax of the primary PCa lesion is correlated with GS, tumor grade, metastatic extent of disease, and serum PSA values [5, 17, 18]. In our study, PSA value was positively correlated with

Table 2. *Correlation between metastatic pattern with SUVmax, SUVmean, PSMA-TV, and TL-PSMA parameters of the primary tumor.*

	Metastatic Pattern			Total	P
	Nonmetastatic	Isolated pelvic lymph node metastasis	Distant metastasis		
	Mean±SS (median)	Mean±SS (median)	Mean±SS (median)	Mean±SS(median)	
SUVmax	19.18±12.5 (16.56)	15.96±14.23 (10.71)	21±14.25 (17.95)	19.48±13.46 (16.56)	0.460
SUVmean	10.23±6.3 (8.16)	8.11±5,24 (6.31)	10.46±5.68 (9.76)	9.98±5.84 (9.19)	0.429
PSMA-TV	5.06±3.36 (3.76)	11±9.21 (8.12)	22.56±33.22 (11.74)	13.99±23.95 (8.12)	0.000*
TL-PSMA	45.39±27.99 (35.50)	102.47±125.64 (44.30)	283.49±502.53 (132.30)	162.96±357.18 (73.88)	0.002*

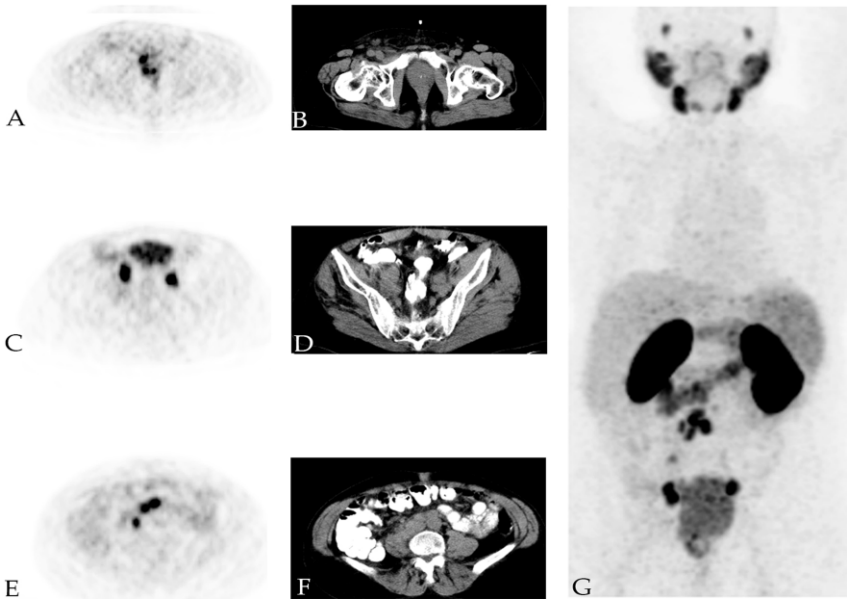

Figure 1. ^{68}Ga-PSMA PET-CT: axial slice PET (A,C,E), axial slice CT (B,D,F) and whole body PET (G) images of a 74-year-old PCa patient with biopsy-proven PCa (GS 4+4) and a PSA value of 1.62ng/mL. Axial slice PET and CT imaging showed PSMA positive primary prostate tumor at the mid and base of the gland (SUVmax value 16.59, SUVmean value 9.36, PSMA-TV 9.95 cm^3 and TL-PSMA 93.1). There were multiple PSMA positive iliac, common iliac and aortocaval lymph nodes compatible with metastases.

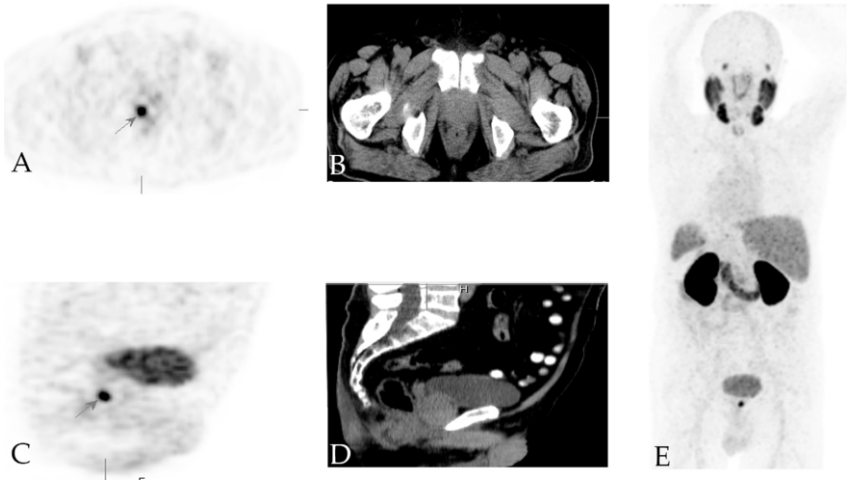

Figure 2. ^{68}Ga-PSMA PET-CT: axial slice PET (A,C), axial slice CT (B,D) and whole body PET (E) images of a 68-year-old PCa patient with biopsy-proven PCa (GS 4+4) and a PSA value of 27.78ng/mL. Axial slice PET and CT imaging showed intense PSMA uptake foci at the right side of the prostate gland (SUVmax value 19.87, SUVmean value 10.89, PSMA-TV 1.34cm^3 and TL-PSMA 14.6). There was no increased PSMA uptake compatible with metastasis.

PSMA-TV and TL-PSMA, but there was no statistically significant correlation found between serum PSA value and SUVmax and SUVmean of the primary tumor.

The main limitations of our study are the retrospective design and the low number of patients. With the aim of creating a homogeneous patient group and focusing on the metabolic parameters of primary tumour in the same group of patients, we only included GS >7 patients in our study. Additionally, the lack of histopathological verification of lesions assessed as metastasis with ^{68}Ga-PSMA PET/CT imaging is another limitation of our study.

In conclusion, the PSMA-TV and TL-PSMA values are strong markers for metastasis prediction in patients with GS >7 PCa but no PSMA expression parameters can distinguish N1M0 and M1 groups.

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