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Relationship between tumor parameters in Ga-68 PSMA PET/CT and pathological grade grouping in patients with prostate cancer

F. Demir[1*], S. Karaçavuş[1], H. Gençer[1], A. Özdal[1], Z. Erdoğan[1], İ. Çiftçi[1], F. Çevik Kaya[2], N. Özhan[3], H. İşçi[1], M. Kaya[1]

[1]Department of Nuclear Medicine, Kayseri Training and Research Hospital, Kayseri, Turkey
[2]Department of Pathology, Kayseri Training and Research Hospital, Kayseri, Turkey
[3]Department of Oncology, Kayseri Training and Research Hospital, Kayseri, Turkey

► ***Original article***

Corresponding author:
Fadime Demir, Ph.D.,
E-mail:
drfadimedemir@hotmail.com

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ABSTRACT

Background: The study aims to explore the relationship between tumor parameters acquired from Ga-68 PSMA PET/CT and GG system in patients who had prostate cancer. ***Materials and Methods:*** One hundred and fourteen patients diagnosed with prostate cancer and who underwent Ga-68 PSMA PET/CT imaging for staging purposes were enrolled. The imaging was performed using a Siemens Biograph Horizon-3R 16 slice PET/CT device, and the tumor parameters (SUVmax, SUVmean, and Tumor volume) were calculated by an experienced nuclear medicine physician. ***Results:*** There was a correlation between GG with SUVmax (p:0.010; r:0.241) and SUVmean (p:0.06; r:0.258). In redicting high-risk patients, ROC analysis was conducted for SUVmax and SUVmean, resulting in significant cut-off values for both parameters. A cut-off value of 9.8 for SUVmax resulted in a sensitivity of 69% and a specificity of 58%. 5.8 cut-off value for SUVmean resulted in 68% sensitivity and 58% specificity. Tumor volume was found to be a significant predictor for distant metastasis. When a cut-off value of 11.53 cm3 was used for tumor volume, sensitivity was found to be 62% and specificity 56%. ***Conclusion:*** According to the results, correlation between GG with SUVmax and SUVmax was significant. Additionally, SUVmax and SUVmean were significant predictors of high-risk prostate cancer, while TV was a significant predictor of distant metastases. In summary, Ga-68-PSMA PET CT are deemed a beneficial imaging modality for both prognosis assessment and staging in clinical.

INTRODUCTION

Prostate cancer is prevalent among men and ranks as the second most common solid tumor. It primarily affects middle-aged men (aged 45-60). Its etiology is heterogeneous, with factors such as family history, age, obesity, diabetes, smoking, and environmental influences being held responsible [1, 2]. Although the Gleason grading system, developed for prostate adenocarcinomas, has been used as a consistent grading system for many years, recent advancements have aimed to maximize patients' quality of life, minimize treatment-related morbidity, and select optimal treatment options by making adjustments to the grading system. The latest revision of the Gleason grading system, as proposed by the International Society of Urological Pathology (ISUP) and accepted in the World Health Organization's (WHO) 2016 classification of prostate tumors, has been published [3- 5]. According to this new International Society of Urological Pathology (ISUP) gleason grouping system (GG), prostate cancer is classified into five groups: GG1 (Gleason score(GS) ≤6), GG2 (GS3+4=7), GG 3 (GS4+3=7), GG4 (GS4+4 =8, 3+5=8, 5 + 3 = 8), GG5 (GS4+5, 5+4, or 5+5) [6].

The treatment of prostate cancer can be challenging in cases of late detection or high metastatic rate. Therefore, predictive biomarkers are of great importance in terms of disease prognosis and metastasis prediction [7]. Prostate-specific membrane antigen (PSMA) that is a transmembrane protein is one of them and highly expressed in prostate cancers. PSMA ligands labeled with ^{68}Ga are increasingly used in Positron Emission Tomography / Computed Tomography (PET/CT) scannig, offering high tumor uptake and image quality [8]. Multiparametric Magnetic Resonance Imaging (mpMRI) is indeed a commonly chosen method for diagnosing prostate cancer due to its ability to provide detailed images of the prostate and surrounding tissues [9], Ga-68-PSMA PET imaging is becoming increasingly popular, especially for the detection of distant metastases and biochemical recurrence [10]. While the consensus regarding the value of Tumor Standardized Uptake Value (SUVmax) in PSMA PET/CT for disease prognosis is not yet clear, recent studies in this field

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have demonstrated a correlation between tumor SUVmax values and pathological grade, providing information into disease prognosis [11]. There are studies showing the benefit of the tumor involvement pattern in PSMA PET CT for the detection of malignancy and its contribution to determining the biopsy area. In fact, they have stated that in patients where a biopsy has not been performed but high likelihood of prostate cancer is suspected, starting the treatment process after PSMA PET CT can be done without the need for biopsy, reducing the complications of biopsy [12-14]. Furthermore, it has proven to be a sensitive imaging method for detecting prostate cancer recurrence, even at very low PSA levels [15, 16].

The aim of this study was to examine the correlation between the tumor parameters obtained from PSMA PET/CT and GG in patients with prostate cancer. Thus, we aimed to demonstrate how the histopathological structure of the tumor affects tumor uptake in PSMA PET/CT. As a result, we aimed to contribute to the diagnosis and prognosis of patients before or after biopsy, as well as contribute to the relatively few studies in the literature in this field.

MATERIALS AND METHODS

Patients

Subjects diagnosed with prostate cancer who underwent PSMA PET/CT imaging for staging between October 2019 and December 2021 were enrolled. The study commenced following approval from the institutional ethics committee (decision number: 601). The GS and ISUP GG values from the biopsy results performed under transrectal ultrasound (TRUS) guidance at the time of diagnosis were recorded. Grade groups are reported according to Gleason grading system, as proposed by the ISUP classification of prostate tumors [4]. Serum PSA values obtained within a maximum of 1 month of imaging were also recorded. Metastasis decision was made with the correlation with conventional imaging methods after PET/CT, PSA values and clinical findings. Biochemical and sociodemographic data of the patients were obtained from the hospital archives. Patients with incomplete data or unavailable PET/CT images were excluded from the study.

Ga-68 PSMA PET/CT protocol

PSMA PET/CT scan was conducted 60 minutes after intravenous injection, with dosages adjusted to the patients' body weights, ranging from 1.8 to 2.2 MBq/kg. Siemens Biograph Horizon-3R 16 slice PET/CT (Siemens, Knoxville,Tennessee, USA) device was used for imaging. PET images were obtained in the supine position from the vertex to the legs, with a duration of 2 minutes per bed position. Attenuation correction was performed using contrast-free low-dose CT images (130 kVp, 142 mAs, a slice thickness of 5 mm).

Ga-68-PSMA PET/CT image analysis

PET/CT images were loaded onto workstations (Siemens Syngo.via VB10B; Knoxville,Tennessee, USA), and SUVmax related to the tumor tissue in the prostate were calculated automatically using the region of interest including the tumor tissue, as determined by an experienced nuclear medicine physician. The SUVmean and TV of the lesion were automatically calculated, using a 41% SUV threshold.

Statistical analysis

SPSS 20.0 were employed to make all Statistical analyses (SPSS Inc, Chicago, IL). The relationship between PET/CT parameters and GG classification was analyzed using Spearman correlation analysis. Student t-test, Mann-Whitney U test, and chi-square test were employed to compare the parameters between the low-intermediate and high-risk patient groups. Receiver Operator Characteristic (ROC) analysis was conducted to determine the predictive value of the parameters for identifying the high-risk group, and the area under the curve (AUC) and cut-off values were calculated. Additionally, a characteristic ROC analysis was performed to determine the predictive value of the parameters for distant metastasis, and the AUC along with the cut-off values were calculated. $P < 0.05$ was considered to statistical significance.

RESULTS

One hundred and fourteen subjects with prostate cancer were enrolled in the study. The mean age was 68±8 years. Among the patients, metastasis of lymph node was not observed in 46 (40%), while 68 (60%) had lymph node metastasis. Of the patients with lymph node metastasis, 61 (90%) had pelvic metastasis and 7 (10%) had extrapelvic lymph node metastasis. In 36 (32%) patients, there were no lesions in extraprostatic organs, while in 78 (68%) patients, such lesions were present. The extraprostatic organ involvements were observed in 38 (33%) patients in the bone, 29 (25%) in the seminal vesicles, 5 (4.4%) in the penis, and 3 (3%) in the lungs, while 3 (3%) patients had metastatic lesions in multiple organs. Looking at the GS, 10 (9%) patients had GS6, 31 (27%) had GS7, 29 (25%) had GS8, 36 (32%) had GS9, and 8 (7%) had GS10. When we look at the ISUP GG, 9 patients (8%) were included in GG1, 17 patients (15%) were in GG2, 14 patients (12%) were in GG3, 30 patients (26%) were in GG4, and 44 patients (39%) were in GG5. The age, SUVmax, SUVmean, Tumor volume, and PSA values of patients grouped according to GG are summarized in table 1.

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Table 1. Age, tumor SUVmax, SUVmean, TV, and PSA values of patients according to the GG classification.

Grade Grup (mean±SD)	**1 (n=9)**	**2 (n=17)**	**3 (n=14)**	**4(n=30)**	**5(n=44)**
Age (mean±SD)	64±9	66±5	70 ±5	69±8	69±8
SUVmax Med (Min–Max)	8.72 (3.37-84.11)	9.06 (2.93 - 38.01)	12.88 (4.34-19.93)	12.65 (2.24-48.45)	15.58 (2.16-1.03)
SUVmean Med (Min–Max)	5.34 (1.83 - 57.59)	5.21(1.70 -21.88)	7.58 (2.38 - 11.96)	7.22 (1.27-33.40)	9.20 (1.07-37.28)
TV_{cm3} Med (Min–Max)	3.00 (0.56 - 11.63)	5.64 (1.24-17,31)	7.49 (0.66-19.19)	3.86 (1.27-12.24)	4.29 (0.51-32.65)
PSA Med (Min–Max)	1.10 (0.001-2)	1.10 (0.001-20)	1.90 (0.001-50)	1.70 (0.001-50)	6.00 (0.001-50)

SUVmax (maximum standardized uptake value), SUVmean (mean standardized uptake value), TV (tumor volume in PSMA-PET/CT), PSA (prostate-specific antigen (ng/ml))

When examining the correlation between GG and SUVmax, SUVmean, and TV values, there was a significant but weak correlation between SUVmax (p=0.010; r=0.241) and SUVmean (p=0.006; r=0.258) values with the GG (figure 1), while there was no correlation with TV (p>0.05).

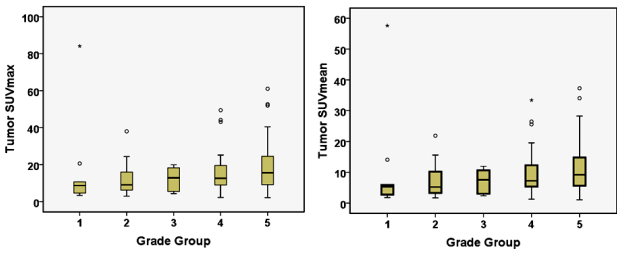

Figure 1. Correlation analysis graph of pathological GG with SUVmax and SUVmean values. Pearson ρ 0.241; 0.258 (P<0.05).

When the subjects were categorized into low-intermediate and high-risk groups according to the GG, significant differences were observed in age, SUVmax, SUVmean, and PSA values between these two groups. However, there was no statistical significance regarding TV. The values of parameters in the groups and whether there is a difference between the groups are summarized in table 2. In figure 2, PSMA PET/CT images of two patients, one from the low-risk group and one from the high-risk group, are presented.

In the prediction of pathological high-risk patients, when ROC analysis was performed for SUVmax and SUVmean values, significant cut-off values were calculated for both parameters (figure 3). When a cut-off value of 9.8 was taken for SUVmax, the sensitivity was 69% and the specificity was 58% (AUC: 0.637, p=0.034). When a cut-off value of 5.8 was taken for SUVmean, the sensitivity was 68% and the specificity was 58% (AUC: 0.637, p=0.034).

When examining the ability of PSMA PET/CT tumor parameters to predict lymph node metastasis or distant metastasis, none of the three parameters had a significant predictive value for lymph node metastasis (p>0.05). However, for predicting distant metastasis, only tumor volume had a significant predictive value (p=0.030; AUC: 0.63) (figure 4). When a cut-off value of 11.53 cm3 was taken for TV, the sensitivity was 62% and the specificity was 56%.

Table 2. Comparison of parameters in patients of low and intermediate-risk groups.

	Low-medium Risk Group	**High Risk Group (n=40)**	**p value (n=74)**
Age (mean±SD)	67±6	69±8	0.182
SUVmax Med (Min–Max)	8.89(2.93-84.11)	13.91 (2.16-61.03)	0.017
SUVmean Med (Min–Max)	5.27(1.70-57.59)	8.41(1.07-37.28)	0.014
TV_{cm3} Med (Min–Max)	5.02(0.56-17.31)	4.16(0.51-32.65)	0.428
PSA Med (Min–Max)	1.38(0.001-50)	3.84(0.001-50)	0.002
Lymph node metastasis (n)	16	52	0.002
Extra-prostate organ involvement (n)	21	57	0.007

SUVmax (maximum standardized uptake value), SUVmean (mean standardized uptake value), TV (tumor volume in PSMA-PET/CT), PSA (prostate-specific antigen (ng/ml))

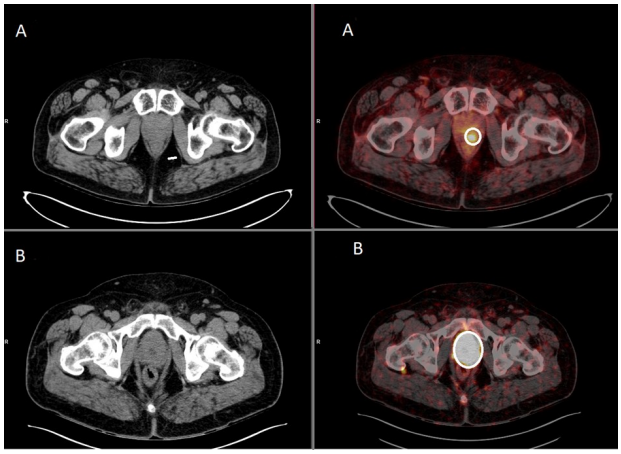

Figure 2. PSMA PET/CT images of two patients in the low-risk **(A)** and high-risk **(B)** groups. **A)** The SUVmax of the primary tumor in the patient from the low-risk group (GG 2) was 7, while **B)** the SUVmax of the primary tumor in the patient from the high-risk group (GG 5) was 30.

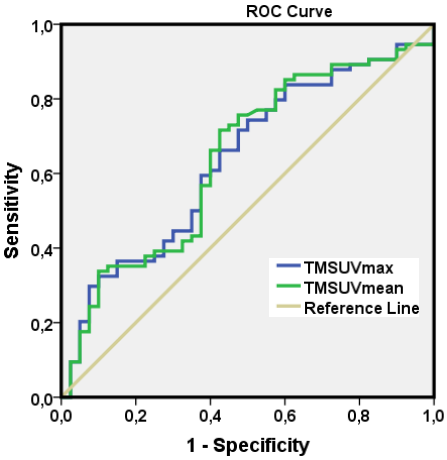

Figure 3. ROC Curve of SUVmax and SUVmean values in predicting the high-risk group.

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DISCUSSION

The Gleason grading system was first used by the Veterans Affairs Cooperative Urological Research Group (VACURG) in patients with prostate cancer. Its goal was to determine the best treatment for prostate cancer and create a grading system [17]. This grading system has undergone many revisions to date and received its final form through a consensus meeting by the ISUP in 2014. The latest National Comprehensive Cancer Network (NCCN) guidelines classify GG 1-2 as low risk, GG 3 as intermediate risk, and GG 4-5 as high risk based on this grading system and PSA values [18].

PSMA that is a type II membrane glycoprotein is highly expressed in primary tumors and metastatic tissues of prostate cancer, with medium to high levels of expression in over 90% of cases [19]. Since the introduction of PSMA PET/CT imaging for prostate cancer, several radiotracers have been tested, with Ga-68 PSMA being the most commonly used. Ga-68 is a cyclotron-produced isotope with a half-life of 68 minutes [20]. PSMA PET/CT has emerged as the preferred imaging technique for restaging, with studies demonstrating its high sensitivity in diagnosing and staging clinically important prostate cancers [21]. When staging the disease, particularly identifying localized disease, it can enable the application of less toxic treatment options [22].

There are studies indicating that the uptake of PSMA in the tumor during PSMA PET/CT is correlated with the GS. One such study is the research conducted by Chen *et al*., where they discovered that PSMA uptake was associated with the GS, T stage, and PSA levels [23]. In the study conducted by Yıldırım *et al*., they also observed a correlation between the parameters of PSMA PET/CT with PSA and the GS, with this correlation being more pronounced in the castration-naive patient group [24]. According to the findings of the study conducted by Uprimny et al., the uptake of 68Ga-PSMA was lower in patients with a GS of 6 and 7 and PSA levels ≤10 ng/ml, but higher in patients with a GS >7 or PSA levels ≥10 ng/ml. Consequently, they asserted that it would yield more accurate outcomes, particularly in this group of patients during the initial staging [25]. There was a correlation between tumor SUVmax and SUVmean values and GG in PSMA PET/CT in our study. Furthermore, SUVmax and SUVmean values in high-risk group patients were significantly higher compared to patients in the low-medium risk group. In the study by Demirci *et al*., they also stated that there is a correlation between GG group and tumor uptake in PSMA PET/CT, and that areas with high intensity of involvement in the prostate gland can be guiding during biopsy [11]. When examining the results of the studies in the literature, we found similar findings to our study, emphasizing the correlation between tumor PSMA uptake in PSMA PET/CT and GS or GG in almost every study. This result supports the use of PSMA PET/CT in both primary staging and characterization of suspicious lesions, and it may lead to reconsideration of the role of PSMA PET CT in these areas. In our study, we also calculated cut-off values for SUVmax and SUVmean, and we showed that when a cut-off value of 9.8 was taken for tumor SUVmax and 5.8 for SUVmean, they had a significant predictive value in predicting high-risk group (GG 4 and 5) patients. In the study by Emre et al., they found a cut-off value of 9 for SUVmax. In the study by Erdoğan *et al*., they found a cut-off value of 10.55 for differentiating intermediate and high-risk groups based on SUVmax [26]. Additionally, in this study, they found a cut-off value of 7.96 for SUVmax, which was a cut-off value for predicting multiple metastases. In the study by Pepe *et al.*, they found a cut-off value of 8 for SUVmax in predicting clinically significant prostate cancer and stated that PSMA PET/CT would provide significant contribution in both staging and diagnosis in this patient group [27]. In the study by Dong et al., they found a cut-off value of 9.6 for predicting high-risk patients using SUVmax. In this study, they also calculated a cut-off value of 10.27 within the tumor volume. Additionally, it did not have a significant predictive value in predicting high-risk patients [28]. In our study, we did not find a significant correlation between tumor volume and GG. However, in our study, the TV was significantly higher in patients with distant metastasis compared to those without. Additionally, when a cut-off of 11.53 cm3 was taken for TV, it had a significant predictive value for distant metastasis. In the study conducted by XIE et al., they found that the PSMA-TV (PSMA-TV) and Total Lesion-PSMA (TL-PSMA) were significantly higher in patients with distant metastasis. PSMA-TV and TL-PSMA values were notably elevated in the high-risk prostate cancer group compared to the low-intermediate risk group [29]. The results were similar to our study.

The retrospective nature of this study and also fairly small patients population are limitations of tghe present study.

CONCLUSION

Our study has demonstrated a correlation between the tumor's PSMA uptake in PSMA PET/CT and Gleason Grade (GG), showing significant predictive value, particularly in predicting high-risk prostate cancer. To this end, the utilization of cut-off values of 9.8 for SUVmax and 5.8 for SUVmean can serve as guiding parameters. Furthermore, PSMA-TV exhibited significant predictive value for distant metastasis. In conclusion, we contend that PSMA PET/CT constitutes a valuable imaging modality for both prognosis determination and staging in clinical practice.

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***Author contributions statement*:** F.D. Protocol/ project development, data analysis, manuscript writing/editing; S.K. Protocol/project development, data analysis, manuscript writing/editing, H.G., A.Ö., Z.E., İ.Ç., F.Ç.K., N.Ö., H.İ., M.K. Data collection or management.

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