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Confirmation of PSMA expression measured on [^{68}Ga]Ga-PSMA PET/CT by immunohistochemistry in prostate adenocarcinoma

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Abstract

Background: Our aim is to determine the accuracy of [^{68}Ga]Ga-PSMA PET/CT in showing PSMA expression in primary prostate cancer and to investigate the relationship between SUVmax and immunohistochemical PSMA expression, Gleason score, and PSA value.

Material and methods: We retrospectively analyzed 66 male patients who were diagnosed with primary prostate adenocarcinoma, underwent pre-treatment [^{68}Ga]Ga-PSMA PET/CT examination for staging, and performed radical prostatectomy between March 2018–August 2020. Immunohistochemical staining was applied to the radical prostatectomy specimens of all patients to detect PSMA expression. The results were evaluated as an immunoreactive score (IRS) and a modified IRS was obtained. Gleason score groups and prostate-specific antigen (PSA) serum values of the patients were obtained from the patient files.

Results: The high SUVmax of primary prostate tumors was significantly correlated with a high modified IRS score (score 2; 3), high PSA value, high Gleason score, and metastasis. In correlation analysis, a positive correlation was found between SUVmax and PSA value and modified IRS score ($r = 0.69$, $p = 0.001$; $r = 0.39$, $p = 0.001$). In addition, there was a statistically significant weak correlation between PSA serum concentration and modified IRS scores ($r = 0.267$; $p = 0.03$). In regression analysis, the percentage of positive cells had a statistically significant and increasing effect on SUVmax ($p = 0.031$; std beta = 0.268; 95% CI = 0.231–4.596).

Conclusions: In prostate adenocarcinoma, SUVmax of the primary tumor in [^{68}Ga]Ga-PSMA PET/CT correlates with immunohistochemical PSMA expression. In addition, high SUVmax is associated with markers of poor prognoses, such as high PSMA expression, PSA value, and Gleason score.

KEY words: prostate adenocancer, SUVmax, [^{68}Ga]Ga-PSMA PET/CT, immunohistochemistry, Gleason score, PSA

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Introduction

Prostate cancer is the second most common cause of death in men after lung cancer among malignant diseases. Although the incidence increased significantly with prostate-specific antigen (PSA) screening, the risk of death was decreased by only 1% [1]. PSA screening, transrectal ultrasound, biopsy, and histopathological evaluation are used in the diagnosis [2, 3]. Based on the guidelines, magnetic resonance imaging (MRI), computerized tomography (CT), and bone scintigraphy [4, 5]. As it is known, prostate-specific membrane antigen (PSMA) is a type-2 transmembrane protein in different tissues such as the prostate gland, kidneys, salivary glands, glial cells, and jejunum [6]. It is highly expressed in cell membranes in prostate cancer [7]. It has been reported that PSMA expression is associated with survival in prostate cancer [8]. However, there may be inter- and intra-patient heterogeneity [9]. Higher uptake of [^{68}Ga]Ga-PSMA in primary prostate cancer and

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metastases is associated with PSMA expression, and it is reported that high PSMA expression is associated with poor prognosis. It has also been reported that high PSMA expression is correlated to a high Gleason score (GS), which is associated with poor prognosis [10–12]. The maximum standardized uptake value (SUVmax) is a semiquantitative parameter that reflects PSMA expression. The SUVmax of prostate cancer in [68Ga]Ga-PSMA PET/CT is four times higher than normal prostate tissue [13]. Whether or not radiolabeled-PSMA expression correlated to the actual PSMA expression is controversial, and there has been a limited number of studies about the issue [14, 15].

We aimed to analyze the power of [68Ga]Ga-PSMA PET/CT for detecting PSMA expression in primary prostate cancer cells, and the relationship between SUVmax and immunohistochemically determined PSMA expression, GS, and PSA serum levels.

Material and methods

Patients

This retrospective study was conducted on patients diagnosed with prostate adenocarcinoma who underwent [68Ga]Ga-PSMA PET/CT for staging between March 2018 and August 2020. Among these patients, 66 males (mean age: 64.48 ± 7.63 years; range: 45–84 years) who underwent radical prostatectomy after [68Ga]Ga-PSMA PET/CT were included. [68Ga]Ga-PSMA PET/CT was performed at least 2 weeks after the biopsy. Multiparametric prostate MRI (mp-MRI) was performed for primary tumor staging before [68Ga]Ga-PSMA PET/CT. The patients did not receive any treatment before surgery. Histopathological analysis of final postoperative tissue specimens was performed in all patients. In accordance with the 2014 International Society of Urological Pathology recommendations [16], which were later adopted by the WHO for the 2016 edition of Pathology and Genetics, the participants were divided on the basis of GS and grade, as follows: grade group 1 (GS: ≤ 6); grade group 2 (GS: 3 + 4 = 7); grade group 3 (GS: 4 + 3 = 7); grade group 4 (GS: 4 + 4 = 8; 3 + 5 = 8; 5 + 3 = 8); and grade group 5 (GS: 9–10). Of the patients, 22 were (33.3%) in grade group 1; 12 (18.2%) in grade group 2; 7 (10.6%) grade group 3.8 (12.1%) grade group 4 and 17 (25.8%) were grade group 5. PSA values were measured in all patients within 10 days before the [68Ga]Ga-PSMA PET/CT. Total PSA measurements in the serum of the patients were made using the radioimmunoassay method. PSA values before PET/CT were 51.74 ± 211.92 ng/mL (0.375–1658). The study was approved by the Ethics Committee of our institution (60116787-020/49019).

[68Ga]Ga-PSMA PET/CT image protocol

68Ga-labelled DOTAGA (1, 4, 7, 10-tetraazacyclododecane--1-glutamic acid-4, 7, 10-triacetic acid)-conjugated PSMA-I&T ([68Ga]Ga-PSMA-I&T) was synthesized by a qualified radiochemist under the Good Manufacturing Practice laboratory conditions, using a Scintomics synthesis unit (Lindach, Fürstenfeldbruck, Germany). Quality control of the [68Ga]Ga-PSMA-I&T radionuclide was performed by validated high-performance liquid chromatography and thin-layer chromatography according to the methods developed by others and described elsewhere [17]. All patients underwent a single injection of [68Ga]Ga-PSMA-I&T (mean ± SD: 184 ± 48 MBq; range:122–315 MBq). After an uptake time of approximately 60 minutes, image acquisitions were conducted in the supine position. The patients were examined using a dedicated PET/CT scanner (Gemini TF TOF PET-CT; Philips, Cleveland, Ohio, USA; 3D mode, slice thickness of 5 mm, 4 × 4 × 22 mm Lutetium-yttrium oxyorthosilicate crystal, number of crystals 28.336, 256 × 256 matrix, transverse field of view 576 mm, and axial field of view 180 mm). Emission scans were acquired from the knee to the vertex of the skull for 2 minutes per position without intravenous contrast injection. Transmission images were obtained by low-dose CT (50–120 mAs, 90–140 kVp, 16 CT detectors, slice thickness of 5 mm). Attenuation correction was performed for PET images using CT findings and the ordered subsets-expectation maximization algorithm (33 subsets and 3 iterations). PET images were reconstructed by the iterative method. Transverse, sagittal, and coronal sections (5 mm thickness) were created from PET/CT fusion images and evaluated using Philips Fusion Viewer software (ver. 2.1; Philips Healthcare, Best, The Netherlands).

Image analysis

Two nuclear medicine physicians re-evaluated the [68Ga]Ga--PSMA PET/CT images and reached a consensus for all patients. The sites of the primary prostate tumor/tumors were determined on the basis of prostate biopsies. First, we evaluated whether PSMA expression in the primary tumor was visually distinguishable from the surrounding normal prostate tissue. The isocontour method, with a 40% SUVmax threshold, was used to create a volume of interest (VOI) around the tumor. SUVmax was defined as the maximum SUV from a single voxel anywhere within the VOI. In cases where the primary tumor could not be clearly identified on PET images, VOIs were placed in the area where the primary tumor was found on the prostate biopsy. The other areas of the body were then evaluated. For distant metastases, focal uptake higher than the surrounding background activity, and corresponding to any lesion on the CT images, was considered consistent with metastasis. This criterion was based on our clinical experience and is compatible with the literature [18]. SUVmax values of the metastases were determined using the same method as for the primary tumor. Patients were divided into two groups based on the presence or absence of distant metastases.

Pathological evaluation

We analyzed 66 patients with prostate adenocarcinoma who had undergone radical prostatectomy. Hematoxylin and eosin-stained sections of formalin-fixed and paraffin-embedded (FFPE) tissue were re-evaluated to correlate the histopathologic findings with the imaging results. Serial sections (5 μm thick), containing representative tumor tissue enriched with tumor cells, were used for immunohistochemistry (IHC). IHC staining was performed using an ultraView Universal DAB detection kit (Ventana Medical Systems, Oro Valley, AZ, USA) and an automated staining system (BenchMark XT; Ventana Medical Systems). Monoclonal anti-PSMA (clone 3E6, ready to use; Dako SA, Glostrup, Denmark) was used as the primary antibody. The immunohistochemical results are reported as staining intensity and the percentage of positively stained cells based on the immunoreactive score (IRS), using a modified 4-point IRS classification [19] (Tab. 1, Suppl. Fig. 1, 2). The IHC analysis was performed by an independent investigator.

Table 1. Four-Point IRS Classification*

IRS (modified)	Percentage of positive cells	Intensity of staining	IRS (0–12)
0 = negative	0 = no positive cells	0 = no color reaction	0–1 = negative
1 = mild	1 = < 10% positive cells	1 = mild reaction	2–3 = mild
2 = moderate	2 = 10–50% positive cells	2 = moderate reaction	4–8 = moderate
3 = strong	3 = 51–80% positive cells	3 = intensive reaction	9–12 = strongly positive
	4 = > 80% positive cells		

*Modified from Kaemmmerer et al. [19]; IRS — immunoreactive score

Table 2. Patients characteristics

Patients number [n]	66
Age mean ± SD [range]	64.48 ± 7.63 years (45–84)
PSA mean ± SD [range]	51.74 ± 211.92 ng/mL (0.375–1658)
Primary tumor [n (%)]	
Unifocal	28 (42.4%)
Multifocal	38 (57.6%)
Lymph node metastasis [n (%)]	
Pelvic	6 (9.1%)
Extrapelvic	1 (1.5%)
Distant metastasis [n (%)]	
Bone	4 (6.1%)
Other	2 (3.0%)

SD — standard deviation; PSA —prostat spesific antigen

Table 3. Prognostic factors and SUVmax relationship

	N [%] (total 66)	SUVmax (mean ± standard error)	p-value
Grade group			
1	22 (33.3%)	4.59 ± 0.54	
2	12 (18.2%)	10.15 ± 1.68	
3	7 (10.6%)	11.71 ± 3.72	0.010*
4	8 (12.1%)	13.91 ± 3.07	
5	17 (25.8%)	18.34 ± 3.40	
PSA			
<10 ng/mL	29 (43.9%)	5.55 ± 4.56	0.001
>10 ng/mL	37 (56.1%)	15.03 ± 11.31	
Modified IRS			
0.1	12 (18.2%)	7.22 ± 2.19	0.030
2.3	54 (81.8%)	11.79 ± 1.44	
Metastasis			
No	53 (80.3%)	9.53 ± 1.29	0.024
Yes	13 (19.7%)	16.60 ± 3.22	

*p-value for grade group 5 compared to grade group 1; IRS — immunoreactive score; PSA — prostat spesific antigen; SD — standard deviation

Statistical analysis

All statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics 25 software; Armonk, NY: IBM Corp.). Continuous variables were defined by the mean ± standard deviation and categorical variables were defined by number and percent. Shapiro Wilk test was used for the determination of normal distribution. For independent group comparisons, we used the Mann-Whitney U test. Relations between continuous variables were also investigated by Spearman correlation analysis and Linear Regression analysis. Differences between categorical variables were analyzed with Chi-Square analysis. Statistical significance was determined as $p < 0.05$.

Results

The mean age of the 66 male patients was 65 ± 8 years (range: 45–84 years). All patients underwent radical prostatectomy after [^{68}Ga]Ga-PSMA PET/CT. Tumor localization was unifocal in 28 patients (42.4%) and multifocal in 38 (57.6%). The mean serum PSA concentration was 51.74 ± 211.92 ng/mL (range: 0.375–1658 ng/mL). The average SUVmax value of the primary tumor was 10.95 ± 10.15 (range: 1.75–58.73). Detailed patient characteristics are shown in Table 2.

When metastatic patients were evaluated in terms of modified IRS scores; one patient's score was 1, seven patients' scores were 2, and five patients' scores were 3. According to PSMA expression in IHC, patients were divided into low-modified (0 and 1) and high-modified IRS scores (2 and 3) groups. In the high modified IRS group, the SUVmax value of the primary tumor was significantly higher compared to the low modified IRS group (SUVmax: 11.79 ± 1.44 and 7.22 ± 2.19, respectively; $p = 0.03$) (Tab. 3).

SUVmax values of the primary tumor were significantly higher in the high PSA group (>10 ng/mL) compared to the low PSA (<10 ng/mL) group (SUVmax: 15.03 ± 11.31 and 5.55 ± 4.56, respectively; $p = 0.001$) (Tab. 3).

The relationship between grade group and SUVmax value of the primary tumor; the SUVmax of grade group 5 was significantly higher compared to grade group 1 (SUVmax:18.34 ± 3.40 and 4.59 ± 0.54, respectively; $p = 0.01$). Differences between the other grade groups were not statistically significant (Tab. 3).

The SUVmax values of the primary tumor in the metastatic group were significantly higher than those without metastases (SUVmax: 16.60 ± 3.22 and 9.53 ± 1.29, respectively; $p = 0.02$) (Tab. 3).

In the correlation analysis, positive significant correlations of the SUVmax values of the primary tumor with the PSA values and modified IRS scores were found ($r = 0.69$ and 0.39; $p = 0.001$ and 0.001, respectively). In addition, there was a weak but statistically significant correlation between PSA serum concentration and modified IRS scores ($r = 0.267$; $p = 0.03$).

There was a statistically significant moderate positive correlation between the percentage of positive cells and SUVmax values of the primary tumor ($r = 0.368$; $p = 0.003$). In regression analysis, the percentage of positive cells had a significantly positive

effect on SUVmax values of the primary tumor ($p = 0.031$; std beta = 0.268; 95% confidence interval: 0.231–4.596).

Discussion

The PSMA expression level is mild to moderate in normal and hyperplastic prostate tissue and high in adenocarcinomas [20]. PSMA expression in prostate cancer shows heterogeneity. High PSMA expression has been shown to be associated with tumor aggressiveness, metastasis, and recurrence [21]. Detection of PSMA expression by IHC in preparation for prostatectomy is not routinely performed. [68Ga]Ga-PSMA PET/CT is frequently used for the detection of PSMA expression in prostate cancer. In our study, the SUVmax values of the primary tumor in the highly modified IRS (scores of 2 and 3) group were significantly higher than in the low modified IRS (scores of 0 and 1) group. The modified IRS reflects the staining intensity and the percentage of cells with PSMA expression. Few researchers have studied the relationship between SUVmax and IHC-PSMA expression [14, 15]. Woythal et al. [15] found a correlation between IRS and SUVmax, with a significantly higher SUVmax in the group with IRS > 2 compared to that with IRS< 2. Ferraro et al. [14] found a strong relationship between PSMA-negative tumors on IHC and [68Ga]Ga-PSMA PET/CT negativity.

In our study, when examining the relationship between grade groups and SUVmax values of the primary tumor, the SUVmax values of grade group 5 were found significantly higher than grade group 1 (SUVmax: 18.34 ± 3.40 and 4.59 ± 0.54, respectively; $p = 0.01$). On the other hand, there were no statistically significant differences among the other groups. Although this result, the SUVmax values of the primary tumor were lower in grade group 1 compared to grade groups 2–4. Previous studies reported a significant relationship between GS and SUVmax values of primary tumors in [68Ga]Ga-PSMA PET/CT [11, 22–24]. Uprimny et al. [11] found that SUVmax values were lower in grade groups 1–3 compared to grade groups 4 and 5. However, no differences were reported among the groups. Sachpekidis et al. [22] had similar results. In addition, it was pointed out that the mean SUVmax values of the primary tumor in grade group 2 (GS: 3 + 4) and 3 (GS: 4 + 3) were similar. Our findings are consistent with the literature. However, in contrast, there have been also studies reporting no significant relationship between grade group and primary tumor SUVmax values on [68Ga]Ga-PSMA PET/CT [15, 18, 25]. A limited number of patients in these studies may have caused the differences.

The PSA value is an important parameter to detect prostate cancer and determine its prognosis. It is known that a high PSA value at the time of diagnosis is associated with poor prognosis [26]. In our study, the mean PSA value was 51.74 ± 211.92 ng/mL (range: 0.375–1658 ng/mL). In the group with high PSA (> 10 ng/mL), the SUVmax values of the primary tumor were significantly higher than in the group with low PSA (< 10 ng/mL). In a study by Uprimny et al. [11], the PSA cut-off value was determined as 10 ng/dL, similar to our study, and a positive correlation was found between the PSA and SUVmax values of primary tumors. Similar findings have been reported in various studies [14, 22, 23, 25, 27], but the PSA cut-off values were different among these studies. Some of the studies evaluated the SUVmax values of the primary tumors, while others evaluated visual PSMA expression. Despite this, a significant correlation was found between PSA values and

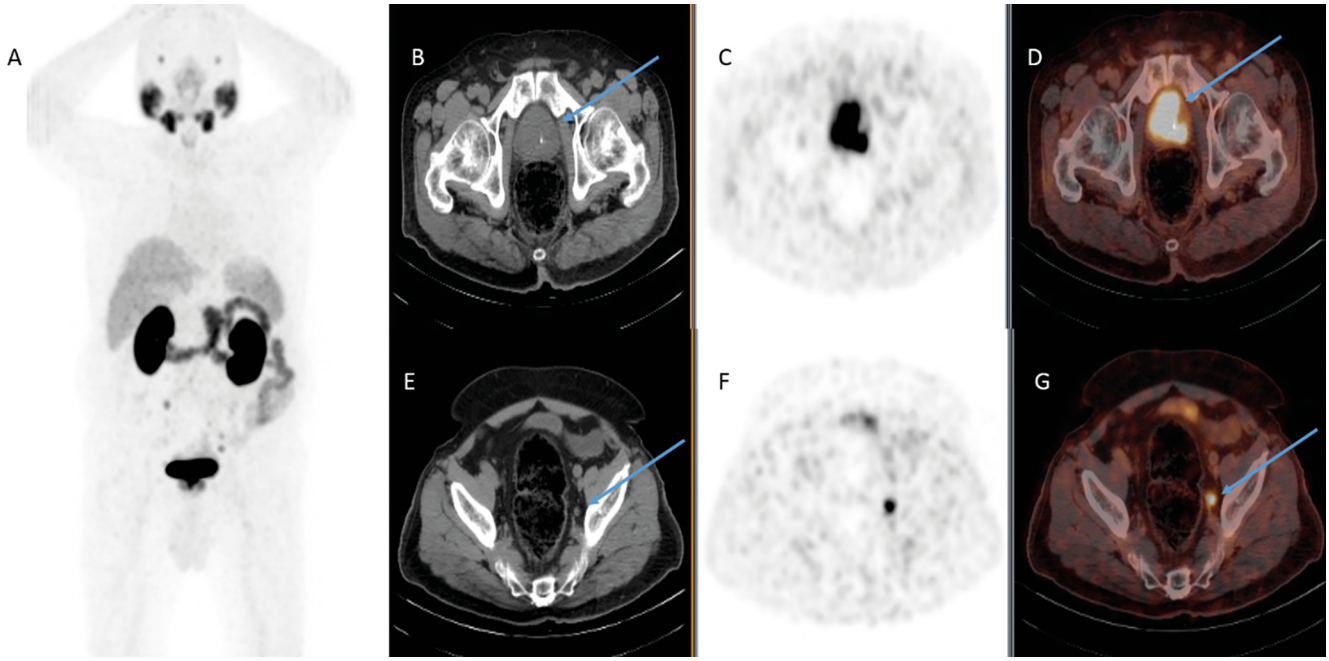

Figure 1. 74 years old man, maximum intensity projection (MIP) [68Ga]Ga-PSMA PET/CT image (**A**); Primary prostate adenocarcinoma (SUVmax: 18.94) is seen in CT, PET, and fusion PET/CT transaxial images (blue arrow) (**B**, **C**, **D**). The left external iliac metastatic lymph node (SUVmax: 6.03) is seen in CT, PET, and fusion PET/CT transaxial images (blue arrow) (**E**, **F**, **G**). Histopathological features of the primary tumor: Gleason score 9, Gleason group 5, PSA: 20.28 ng/mL, modified IRS score 1

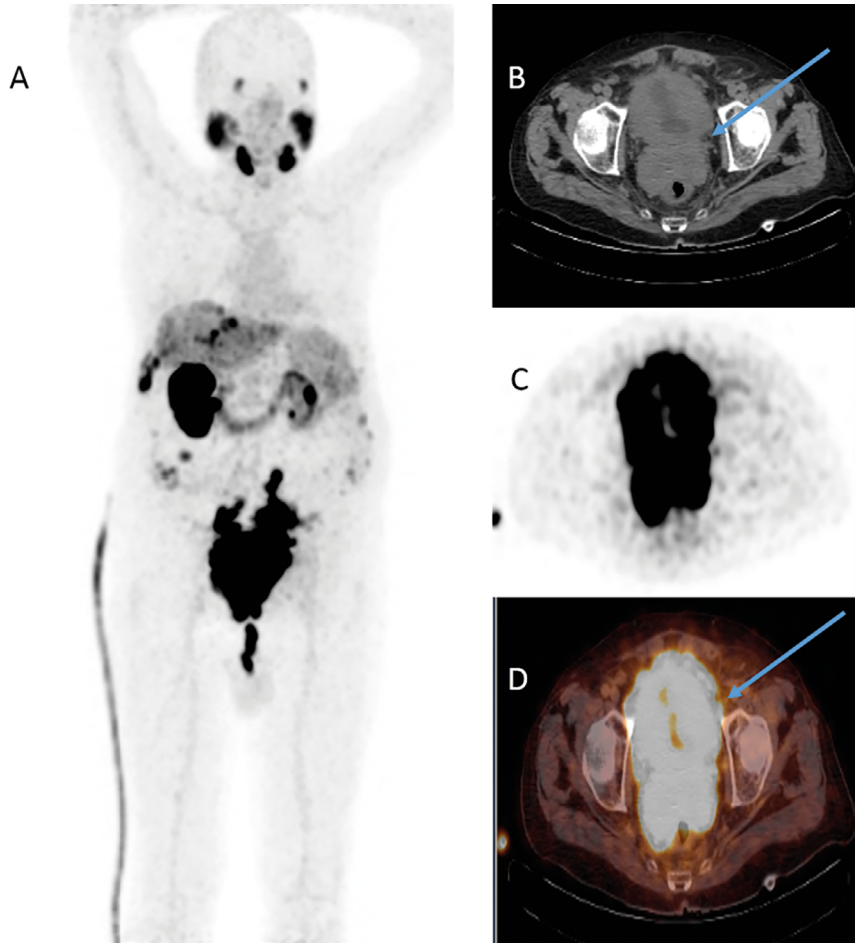

Figure 2. 84 years old man, maximum intensity projection (MIP) [^{68}Ga]Ga-PSMA PET/CT image (**A**). Primary prostate adenocarcinoma invading the bladder (SUVmax: 58.93) is seen in CT, PET, and fusion PET/CT transaxial images (blue arrows) (**B**, **C**, **D**). Histopathological features of the primary tumor: Gleason score 10, Gleason group 5, PSA: 65.78 ng/mL, modified IRS score 2

PSMA expression in [^{68}Ga]Ga-PSMA PET/CT in all studies. In our study, the SUVmax values of primary tumors in the metastatic group patients were significantly higher than those without metastases. High PSMA expression in the primary tumor was associated with tumor aggressiveness, metastatic potential, and recurrence [21]. Few researchers studied the relationship between IHC PSMA expression and the metastatic potential of the primary tumor [21, 28]. However, the relationship between the SUVmax of the primary tumors and metastatic potential has not been studied. In our study, the number of metastatic patients was low (13/66) and these patients could not be evaluated separately because there were very few in the pelvic/extra-pelvic lymph node and distant metastases subgroups. In our study, only 1 patient had modified IRS score 1 (Fig. 1), while 12 of the 13 metastatic patients were high modified IRS scores (scores of 2 and 3) (Fig. 2).

Our study had some limitations. First of all, the [^{68}Ga]Ga-PSMA PET/CT images of the patients were evaluated retrospectively. Secondly, the number of metastatic patients was low. Therefore, pelvic/extra-pelvic lymph node metastasis and distant metastasis subgroups could not be evaluated.

Conclusions

In prostate adenocarcinoma, IHC PSMA expression was positively correlated with SUVmax of primary prostate tumor in [^{68}Ga]Ga-PSMA PET/CT examination. In addition, high SUVmax values of the primary tumor were associated with high-grade group, high PSA values, and metastases. Based on these findings, we conclude that SUVmax values can predict the prognosis of prostate cancer. However, further studies with more patients are required.

Statement of ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients involved in the study have given their written informed consent. The study was approved by the Ethics Committee of our institution (60116787--020/49019).

Conflict of interest

No potential conflicts of interest were disclosed.

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