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Clinical utility of [^{68}Ga]Ga-PSMA-11 PET/CT in initial staging of patients with prostate cancer and importance of intraprostatic SUV_{max} values

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Abstract

Background: As in disease recurrence, providing clinicians with the exact extent of the disease at the time of initial diagnosis is key in the management and individual treatment of prostate cancer (PC) patients. Intending to examine the usefulness of gallium-68 PSMA-11 positron emission tomography/computed tomography ([^{68}Ga]Ga-PSMA-11 PET/CT) and to determine if there is a correlation between prostate-specific antigen (PSA) serum values, WHO/ISUP (World Health Organization/International Society of Urological Pathology's) grade group of the tumor and SUV_{max} (maximized standardized uptake value) values we retrospectively analyzed PET/CT studies performed for initial staging of the disease.

Patients and methods: We retrospectively evaluated 34 studies of patients who underwent [^{68}Ga]Ga-PSMA-11 PET/CT as part of the initial staging of prostate cancer. All patients had prostate cancer confirmed by histological assessment after biopsy and had Gleason score and PSA serum values obtained. The mean PSA value was 33.8 ± 40.9 nmol/L (range 2.2–232).

Results: Nineteen patients had extended disease (55.9%). The mean SUV_{max} in prostate lesions was 19.5 ± 12.6. The mean value of SUV_{max} of PET studies in the high-risk group was significantly higher than those of low risk (23.5 ± 13.2 and 10.6 ± 5.4, $p < 0.05$). A positive correlation was observed between the ISUP group and SUV_{max} value of prostate lesions (Pearson's $r = 0.557$, $p < 0.01$). A positive correlation was also found in the comparison between PSA values and SUV_{max} (Pearson's $r = 0.34$, $p < 0.05$).

Conclusions: In our study, [^{68}Ga]Ga-PSMA-11 PET/CT scans detected the extended disease in more than half of the patients. Locating disease beyond the prostate gland allowed better informed clinical decisions and modified treatment. A positive correlation was found between intraprostatic SUV_{max} values and the ISUP group of prostate cancer. High-risk patients had SUV_{max} values that were significantly higher than those of low-risk patients. The correlation between the Gleason score and SUV_{max} value can be explained by the increased intensity of PSMA expression as the tumor grade increases.

KEYwords: primary staging; [^{68}Ga]Ga-PSMA-11; prostate cancer staging; prostatic SUV_{max} values; PSMA/PET; PSMA expression; ISUP grade groups

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Introduction

According to Global Cancer Data (GLOBOCAN) in 2018 it was estimated that prostate cancer (PC) was the second most common malignancy in the men's population worldwide, accounted for around 15% of all cancers in men, and was the fifth cause of death from malignancies [1]. The most common tests for prostate cancer (PC) screening are analysis of serum for prostate-specific antigen (PSA) and digital rectal examination (DRE). While PSA is organ-specific, it is not cancer-specific and may be elevated in benign prostate hyperplasia, inflammation, and trauma. A high PSA and an abnormal DRE should raise suspicion, and these patients should be referred to the clinic for a biopsy [2, 3].

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Ultrasonography-guided prostate biopsy is a standard for making the primary diagnosis and for risk stratification of prostate cancer. According to pathohistological findings, Gleason grade is assigned based on the most and second most predominant pattern. In 2014 the International Society of Urological Pathology (ISUP) released supplementary guidance and a revised prostate cancer grading system called the Grade Groups — five-grade group system. It is easy to apply and provides important information for the prognosis and therapeutic needs of patients with prostate cancer. Currently, for the extent of disease and staging, guidelines recommend computed tomography (CT) for lymph node (LN) evaluation and bone scan for possible bone metastases (current guidelines of European Association of Urology) [3]. Both methods have severe limitations and may result in under-staging and under-treatment of patients. Computed tomography has low sensitivity for detecting lymph nodes smaller than 8 mm as it cannot differentiate infiltrated from non-metastatic tissue [4]. CT scan does not differentiate between inflammatory lymph nodes and lymph nodes affected by micro-metastases. Magnetic resonance (MRI) has a similar limitation in diagnosing the exact extent of disease in primary staging. Meanwhile, bone scans are usually not very specific and more often cause the need for additional imaging [5].

Choline PET/CT tracers are widely available for high-risk or locally advanced PC patients and should be considered to document potential metastases [6]. However, increased choline uptake in inflammatory tissue and degenerative bone processes heavily limits choline PET/CT specificity.

Accurate prostate cancer staging is key to an individual approach and correct treatment. The primary therapy for patients with clinically significant and localized PC includes radical prostatectomy and external beam radiation therapy. Extended pelvic lymph node dissection (ePLND) is usually indicated for patients who have pelvic lymph node involvement [3].

In the past few years, prostate-specific membrane antigen (PSMA) positron-emission tomography (PET/CT) has been introduced as a valuable tool for urologists in the staging of PC. The impact of PSMA PET/CT on the management of prostate cancer (PCa) in patients with biochemical recurrence (BCR) is well known and established [6, 7] but recently growing numbers of studies [8–11] have shown a profound impact in the initial stage management of PC patients.

Reporting standardized guidelines for PSMA-PET according to the European Association of Nuclear Medicine (EANM) suggest a visual interpretation of images and semiquantitative measurement of PSMA expression with SUV (standardized uptake value). SUV is a mathematically calculated ratio of tissue radioactivity concentration at a different point in time and the injected dose of radiopharmaceutical activity per kilogram of the patient's body weight. In clinical practice, the most used measure of lesion uptake is SUV_{max} This is the SUV in a single pixel with the highest value within a volume of interest. The rationale for this is that the voxel with the highest value should represent the most metabolically active tissue (or tissue with the highest PSMA expression) and particularly for tumors, the tissue of greatest interest. This measurement is easy to implement and is very reproducible [12].

Prostate-specific membrane antigen (PSMA) is a transmembrane protein primarily present in all prostatic tissues. PSMA is a transmembrane protein (glutamate carboxypeptidase II) and it is overexpressed in different kinds of malignancies but most notably in prostate cancer cells, especially in the higher grades group of PC, recurrent PC, and metastatic cancer. In benign prostate tissue, it is only weakly or not at all expressed [13]. Pathohistological and molecular studies have shown that PSMA expression is mostly associated with higher tumor grade [14, 15].

The goal of our study was to examine the usefulness of [68Ga]Ga-PSMA-11 PET/CT in the initial staging of PC and to check for possible correlations between intraprostatic SUV_{max} values and well-established prognostic tumor markers, such as PSA values and International Society of Urological Pathology grade (group) scores.

Patients and methods

Patients

In our retrospective study, we included 34 patients (mean age 69.7 ± 9.8 years) who underwent [68Ga]Ga-PSMA-11 PET/CT scan between April 2021 and January 2023 at the Department of Nuclear Medicine, University Hospital Centre Zagreb. All patients had histologically proven PC in guidelines concurred with the World Health Organization 2016 prostate cancer grading system. The inclusion criteria for the [68Ga]Ga-PSMA-11 PET/CT were: (a) histologically proven primary PC; (b) no treatment before PET/CT; and (c) PSA value measured within one month before the scan.

[68Ga]Ga-PSMA-11 production

68Ga was obtained from 68Ge/68Ga radionuclide generator and complexed with PSMA-11 peptide (on-site using ELYSIA-RAYTEST GAIA SYNTHESIZER, GAIA Peptide Labelling Fluidic Processor (Elysia-ray test GmbH, Germany). Patients were administered [68Ga]Ga-PSMA-11 complex solution via an intravenous bolus injection (mean 206.1 MBq, range 113–308 MBq) according to their body weight (2 MBq/kg).

Image and statistical analysis

Standard image acquisition was performed between 45 and 90 minutes after injection. Low-dose CT images were obtained for both attenuation correction and localization of lesions from the base of the skull to the proximal parts of the thigh with 2–3 minutes of recording per bed position. Images were taken on a Siemens Biograph mCT PET/CT camera (Siemens Medical Solutions USA, Inc., USA). Low-dose computed tomography was recorded at an X-ray tube voltage of 120 kV, X-ray tube current strength of 25 mAs, and the thickness of each layer was 3 mm (pitch 0.8, Kernel B19f) using CARE Dose 4D low-dose CT technology. Acquisition of the 68Ga positron decay signals was recorded with LSO scintillation crystals using "time-of-flight" technology (TOF). PET images were reconstructed using TOF technology and OSEM (ordered subset expectation maximization). PET/CT images were reviewed using a syngo.via workstation (SIEMENS ver. VB60A).

The SUV_{max} value was measured for the most clinically suspect prostatic lesion for semiquantitative analysis. The highest localization of PSMA expression was determined by the highest SUV_{max} spot in the prostate gland. Results and patient characteristics of our study were expressed as mean ± SD, range, and median values. Statistical analysis was performed using software (MedCalc Software, Version 22.003, Belgium, and JASP, Version 0.18.1.0, Netherlands). We used the Pearson's r correlation test for the correlation

Table 1. Summary of clinical and pathohistological characteristics of patients included in our study.

Characteristics	Parameters (n)
Number of patients	34
Age [years] mean [range]	69.7 ± 9.8; (48–88)
ISUP 1 (Gleason 3 + 3)	4
ISUP 2 (Gleason 3 + 4)	8
ISUP 3 (Gleason 4 + 3)	13
ISUP 4 (Gleason 4 + 4)	5
ISUP 5 (Gleason 4 + 5, 5 + 5)	4
Metastatic disease	19/34, 55.9%
Positive lymph nodes	11/34, 32.4%
Bone metastases	7/34, 20.6%
PSA mean [range]	35 ng/mL (2.2–232 ng/mL)
Dose of 68Ga-PSMA administered mean [range]	206.1 MBq (113–310 MBq)

MBq — megabecquerel; PSA — prostate-specific antigen

between SUV_{max} values, and biochemical and prognostic markers. A p-value of equal to or less than 0.05 was considered statistically significant in all our tests.

Results

As expected, all studies were PET positive with increased [^{68}Ga]Ga-PSMA-11 uptake in prostate lesions. In 19 patients extended disease was diagnosed (55.9%). Table 1 summarizes our patients' clinical and pathological characteristics.

WHO/ISUP grade group 1 (Gleason score 3 + 3) was identified in 4 patients, 8 patients belonged to grade group 2 (GS 3 + 4), 13 patients were classified as grade group 3 (GS 4 + 3), 4 patients as grade group 4 (GS 4 + 4), and 4 patients as group 5 (GS 9 and 10). Most of our patients had intermediate or high-risk cancer according to biopsy findings. In low-risk patients, [^{68}Ga]Ga-PSMA-11 PET/CT scan was performed because of inconclusive bone scintigraphy or CT scan to clarify the extent of the disease.

Infiltration of seminal vesicles was found in 12/34 (34.4%) of positive PET studies. Metastases in lymph nodes were observed in 11/34 (32.4%) studies and bone metastases in 7/34 (20.6%). In one patient infiltration was seen in the bladder wall, two patients had metastases in the lungs and one patient had metastasis in a gluteal soft tissue nodule. Primary lung adenocarcinoma concurrent with prostate cancer was seen in one study and later confirmed with pathohistological analysis.

The mean SUV_{max} in prostate lesions was 19.5 ± 12.6. According to ISUP classification, our patients with grade 1 had a mean SUV_{max} of 6.3 ± 1.8, patients in grade group 2 had a mean SUV_{max} of 12.8 ± 5.3, ISUP group 3 had a mean SUV_{max} 19.3 ± 8.7, grade group 4 had the mean SUV_{max} of 29.9 ± 16.9 while grade group 5 had a mean SUV_{max} of 29.2 ± 15. That means that mean SUV_{max} values of low and favorable intermediate-risk patients (ISUP groups 1 and 2) were significantly lower than those of patients in unfavorable intermediate and high-risk groups (ISUP groups 3–5), which were 10.6 ± 5.4 and 23.5 ± 13.3 ($p < 0.05$), respectively. There wasn't a significant difference between intraprostatic SUV_{max} values of local disease limited to a prostate gland against metastatic disease (mean SUV_{max} 17.8 ± 13.3 vs. 21.3 ± 11.3). Representative images of each ISUP group are shown in Figure 1. There was a positive correlation between ISUP groups and the SUV_{max} value of prostate lesions (Pearson's $r = 0.557$, $p < 0.01$) (Fig. 2). A positive correlation was also found in the comparison between PSA values and SUV_{max} (Pearson's $r = 0.34$, $p < 0.05$) (Fig. 3).

No significant correlation between WHO/ISUP groups and PSA values was found [Pearson's $r = 0.26$, p — not significant (ns)]. In patients who had distant metastases mean PSA was 43.9 ng/mL (range 2.2–232 ng/mL) while in a group with only local disease mean PSA was significantly lower — 21.1 ng/mL (range 4.1–53 ng/mL) ($p = 0.008$).

Nineteen patients had some kind of conventional imaging done before the [^{68}Ga]Ga-PSMA-11 PET/CT scan (13 patients had bone scintigraphy and CT while three patients had CT only). Eight patients had pathological uptake of [^{99m}Tc]Tc-MDP seen on bone scans, but only two of those studies had PSMA-positive bone lesions. The rest of the positive bone scan patients were false positives and had no pathological [^{68}Ga]Ga-PSMA-11 uptake seen on PET/CT. In the other five patients with bone metastases reported on [^{68}Ga]Ga-PSMA-11 bone scan was negative.

After the PET/CT scan, all patients were presented to our hospital multidisciplinary team to select the preferred and best personal treatment modality. Out of 11 patients who had disease limited to the prostate, prostatectomy was selected in three cases, in patients in low or intermediate-risk groups. In the follow-up of those patients 6 months after surgery PSAnadir was below 0.1 ng/mL. In two patients with PET-positive lesions in pelvic lymph nodes prostatectomy and lymphadenectomy were performed. Histology confirmed metastases in PET-positive lymph nodes in both cases. In other patients with local disease radical radiotherapy and ADT (androgen deprivation therapy) were selected. In two patients with bone metastases, chemotherapy was added in combination with radical radiotherapy and ADT. Stereotactic body radiation therapy (SBRT) in addition to RT and ADT was chosen in patients with isolated bone metastasis.

Discussion

A recent proPSMA study from Hofman et al. [10] showed superior accuracy of [^{68}Ga]Ga-PSMA-11 PET/CT compared to conventional combined imaging (CT and bone scan). A meta-analysis by Chow et al. [11] found a higher sensitivity (98.0% *vs.* 73.0%) and specificity (96.2% *vs.* 79.1%) of PSMA-labelled tracers for the detection of bone metastases compared to bone scintigraphy. The low specificity of bone scintigraphy may lead to the over-staging of some high-risk patients who would benefit more from radical treatment choices, as we noticed in our study, only 25% of patients with a positive bone scan had an actual PSMA avid bone lesion. In contrast, under-staging is also an issue as it leaves metastases untreated and may lead to poor treatment choices and outcomes.

In the same meta-analysis, Chow et al. [11] showed that the specificity of PSMA PET/CT for the detection of lymph node metastases was consistently high across the included studies, with a mean of 96%. We had limited data on comparing [^{68}Ga]Ga-PSMA-11 PET/CT findings with a pathological sampling of pelvic nodes, but in our two cases, positive PET nodes correlated

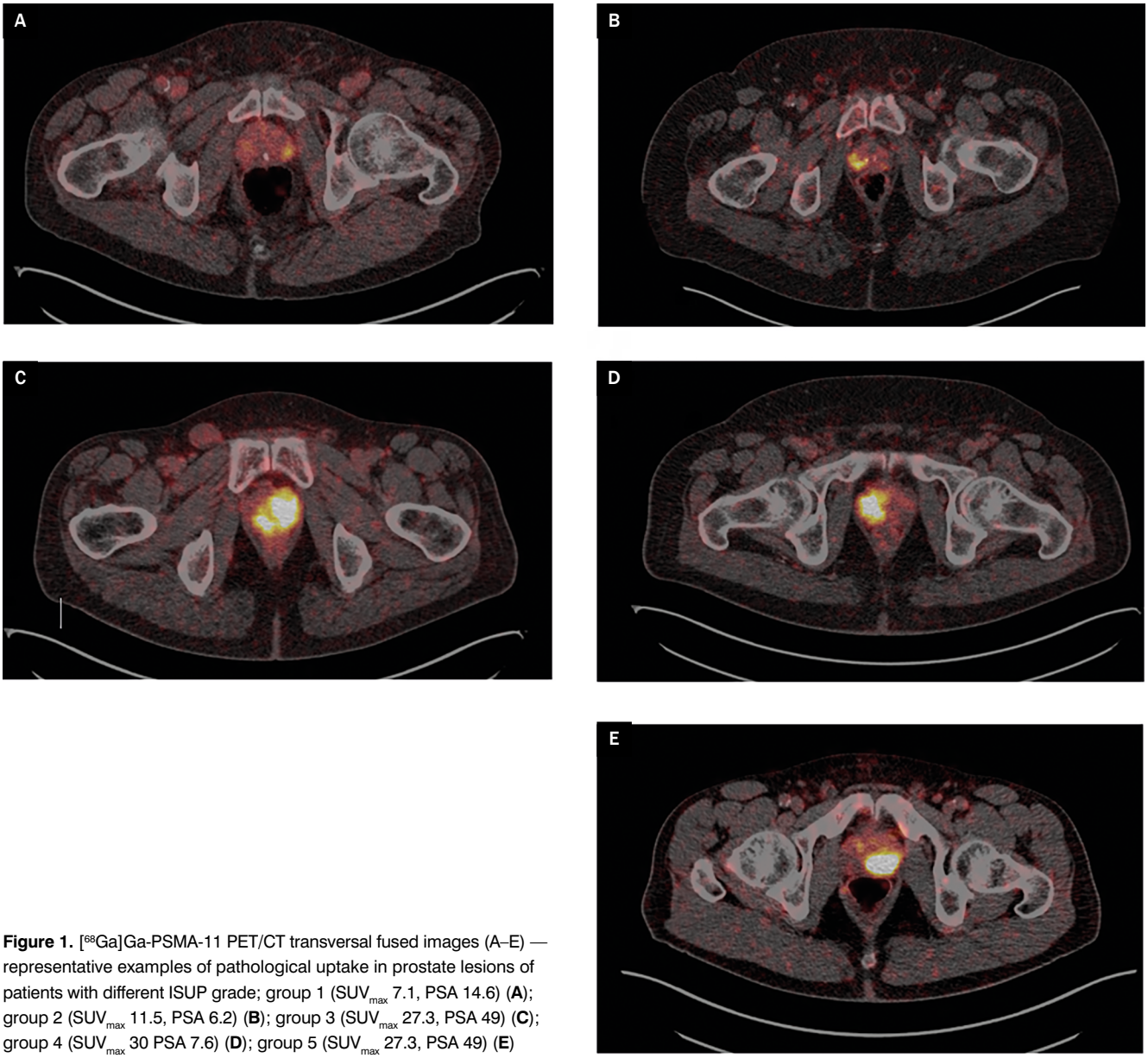

Figure 1. [68Ga]Ga-PSMA-11 PET/CT transversal fused images (A–E) — representative examples of pathological uptake in prostate lesions of patients with different ISUP grade; group 1 (SUV_{max} 7.1, PSA 14.6) (**A**); group 2 (SUV_{max} 11.5, PSA 6.2) (**B**); group 3 (SUV_{max} 27.3, PSA 49) (**C**); group 4 (SUV_{max} 30 PSA 7.6) (**D**); group 5 (SUV_{max} 27.3, PSA 49) (**E**)

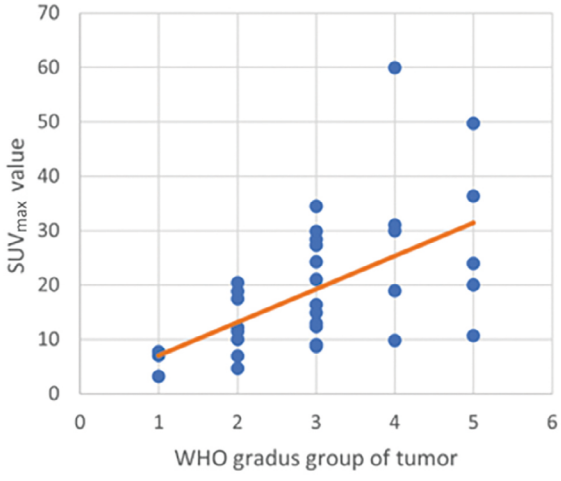

Figure 2. Scatter graph showing a moderate correlation between the WHO group and SUV_{max} values in prostate lesions (Pearson's $r = 0.557$, $p < 0.01$)

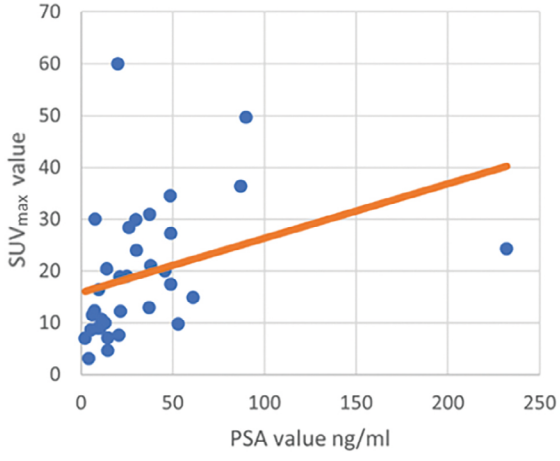

Figure 3. Scatter graph showing positive correlation between serum SUV_{max} and PSA values in prostate lesions (Pearson's $r = 0.34$, $p < 0.05$)

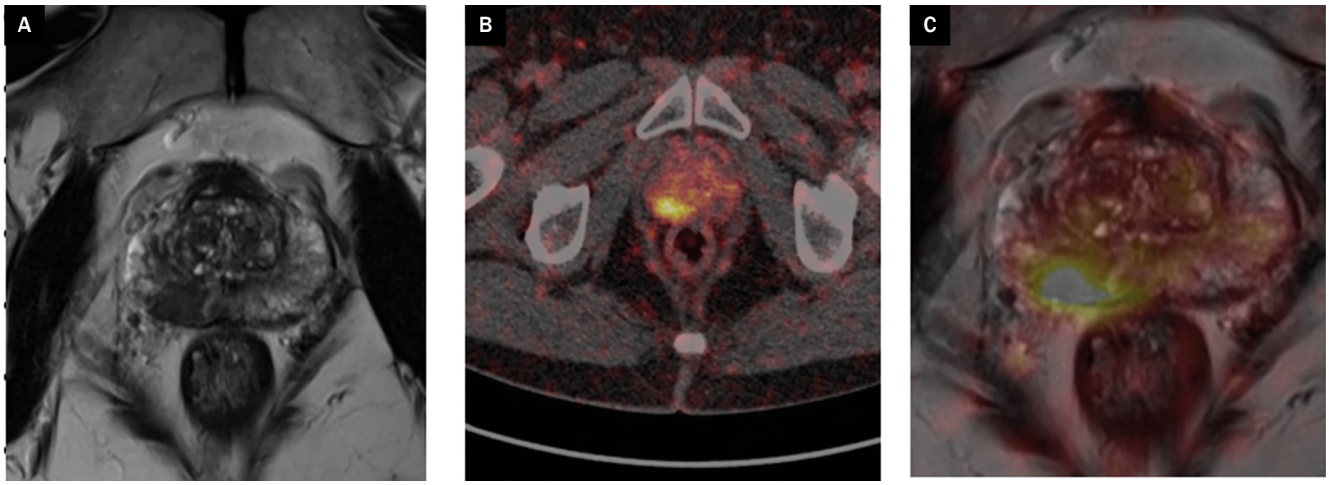

Figure 4. [^{68}Ga]Ga-PSMA-11 PET/MR fusion; transversal T2 MR image of the prostate (**A**); [^{68}Ga]Ga-PSMA PET/CT fused transversal image (**B**) and software fused image of those two methods (**C**) showing exact overlap of lesion visible on MR T2 with pathological uptake of [^{68}Ga]Ga-PSMA-11; before MR patient had negative biopsy and was referred to us with a goal of localizing the tumor and eventual disease spread (PSA 7,35 ng/mL, ISUP grade group 3, Gleason score 4 + 3 = 7)

to nodal metastasis found on histological analysis after lymphadenectomy. Also, in three cases where we found disease limited only to the prostate, PSA nadir in the follow-up after prostatectomy of all patients was below 0.1 ng/mL.

Higher PSMA expression is associated with the higher and more aggressive ISUP grade group. Studies by Silver et al. and Perner et al. [15, 16] showed that with higher pathologic grade and in poorly differentiated cancers expression of PSMA increases. Our study has shown a significant difference between SUV_{max} values of unfavorable intermediate and high-risk patients (ISUP groups 3–5) and those of low-risk and favorable intermediate patients (ISUP groups 1 and 2). This is an important finding to keep in mind, as it shows that higher SUV_{max} could be linked with a higher Gleason score of cancer, and with that with higher aggressiveness of tumor. Similar findings were found in studies by Demirci et al. [17] utilizing [^{68}Ga]Ga-HBED-CC PSMA and Bodar et al. [18] with [^{68}Ga]Ga-PSMA-11.

No positive correlation was found between PSA values and Gleason scores, probably due to the relatively small number of patients. There was a significant difference between PSA values in patients with distant metastases and patients with only localized disease, meanwhile, there was no difference in prostatic SUV_{max} values in those two groups.

Some studies have shown inconsistency between the Gleason score after prostatectomy and definitive pathology analysis and the Gleason score taken from samples in biopsy [19, 20]. There are also cases of repeated false negative biopsies, while definitive pathology has found cancer tissue, some tumor locations inside the prostate gland like apex or anterior parts are simply susceptible to false negative biopsies [21]. SUV_{max} of [^{68}Ga]Ga-PSMA-11 in primary cancer was significantly higher than normal prostate tissue, allowing tumor localization in the prostate, especially in combination with multiparametric magnetic resonance imaging (mpMRI) (Fig. 4). This observation could help better tumor spotting for a more precise preoperative biopsy.

The study had several limitations stemming from its retrospective nature, particularly due to the diverse patient population. The study sample was drawn from routine clinical practice at our department. Another possible limitation is the variability of PSMA ligand accumulation resulting from differences in uptake times of [^{68}Ga]Ga-PSMA-11 across our studies, which may have affected the detection of pathological lesions. This was compounded by the need to administer 2–3 doses of [^{68}Ga]Ga-PSMA-11 at the same time point and one available PET/CT scanner resulting in a range of uptake times. Nevertheless, all our patients had [^{68}Ga]Ga-PSMA-11 uptake time within the recommended range according to EANM guidelines (50 to 100 min) [12]. Furthermore, Wen et al. [22] utilizing [^{68}Ga]Ga-PSMA-11 demonstrated that SUV_{mean} values for pathological lesions at both 35–59 min and 60 min post-injection were similar, while van der Sar et al. [23] found that a shorter time interval of 45 min instead of 60 min between [^{68}Ga]Ga-PSMA-11 administration and PET/CT acquisition had a significant but a small impact on image quality and lesion detection.

The lack of histopathologic confirmation in cases of distant metastases limited our ability to determine the specificity of [^{68}Ga]Ga-PSMA-11 PET/CT, but that was not the focus of this study. Obtaining reliable biopsy results of prostate cancer metastases detected on PET/CT is a widely recognized challenge, even in prospective studies. Therefore, possible false-positive findings cannot be disregarded.

Conclusions

In our study, a positive correlation was found between intraprostatic SUV_{max} values and the ISUP grade of prostate cancer. The correlation between the grade of the tumor and SUV_{max} values can be explained by the increased intensity of PSMA expression as the tumor grade increases. SUV_{max} values of intermediate and high-risk patients were significantly higher than those of low-risk

patients, supporting the usage of [68Ga]Ga-PSMA-11 PET/CT in the initial staging of prostate cancer.

Article information and declarations

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None.

Author contributions

The authors listed have made substantial contributions to the intellectual content of the paper in the various sections described below. IR — conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis; DH, ATG, MG. ZK — supervision; MZ, TS, NJ — administrative, technical, or material support.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics statement

All patients signed written informed consent before undergoing PET/CT scan.

Conflicts of interest

Authors have no conflict of interest to declare.

Supplementary material

None.

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