⁶⁸Ga-PSMA PET/CT Imaging Predicting Intraprostatic Tumor Extent, Extracapsular Extension and Seminal Vesicle Invasion Prior to Radical Prostatectomy in Patients with Prostate Cancer

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Abstract

Purpose ⁶⁸Ga-labeled prostate-specific membrane antigen (PSMA) ligand positron emission tomography/computed tomography (PET/CT) has shown promising results in patients with biochemical recurrence after primary therapy for prostate cancer. In this study, we evaluated the usefulness of PSMA I&T (imaging and therapy) PET/CT prior to radical prostatectomy.

Methods The study population consisted of 21 patients with prostate cancer who underwent ⁶⁸Ga-PSMA I&T PET/CT before either open or laparoscopic radical prostatectomy. Intraprostatic tumor extent, extracapsular extension (ECE) and seminal vesicle invasion (SVI) were assessed on the PET/CT scans. Tracer uptake was quantified in terms of standardized uptake values (SUVs). Imaging findings were correlated with final whole-gland histopathology.

Results Of the 21 patients, two had T stage 2b disease, nine stage 2c, six stage 3a and four stage 3b. The median Gleason score was 7. The SUV_{mean} of the primary tumors was 9.5 ± 8.8. SUV_{mean} was higher in tumors with ECE than in organ-confined tumors (13.8 ± 11.0 vs. 5.6 ± 3.2, *p* = 0.029). Peak tracer uptake was significantly positively correlated with Gleason score (*r*_s = 0.49, *p* = 0.025). Sensitivity, specificity, positive predictive value and negative predictive value were, respectively, 94.7%, 75.0%, 97.3% and 60.0% for tumor infiltration of an individual prostate lobe, 75.0%, 100.0%, 100.0% and 97.4% for SVI, and 90.0%, 90.9%, 90.0% and 90.9% for ECE, using an angulated contour of the prostate as the criterion. Tumor volume derived from ⁶⁸Ga-PSMA I&T PET/CT was significantly correlated with preoperative prostate-specific antigen value (*r*_p = 0.75, *p* < 0.001) and tumor volume on histopathology (*r*_p = 0.45, *p* = 0.039).

Conclusions ⁶⁸Ga-PSMA I&T PET/CT prior to radical prostatectomy can contribute to presurgical local staging of prostate cancer. In this pilot study, ⁶⁸Ga-PSMA I&T PET/CT showed promising results for prediction of lobe infiltration, ECE and SVI.

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Keywords Prostate-specific membrane antigen (PSMA) · PET/CT · Prostate cancer · Staging · Seminal vesicle · Extracapsular extension

Introduction

Prostate cancer is the most frequent malignancy in men worldwide and an increasing incidence has been noted in recent years [1]. Precise assessment of the tumor stage is crucial for therapy planning, and radical prostatectomy is a widely used

potentially curative option [2]. Treatment is most likely curative when the T stage is T2c or less, that is, when extracapsular extension (ECE; stage T3a or more), seminal vesicle invasion (SVI; stage T3b), and metastatic disease (N+ and/or M+) are not present [3–5]. Patients with ECE are at greater risk of lymph node or bone metastases and tumor recurrence after prostatectomy [4]. Moreover, these patients cannot be subjected to bilateral nerve-sparing surgical techniques, increasing the risk of urinary incontinence and erectile dysfunction after prostatectomy [2]. SVI is associated with an increased risk of lymph node metastasis and tumor recurrence in patients with prostate cancer, and its presence at the time of diagnosis is an important factor in prognosis assessment and patient treatment [5]. Conventional methods of staging based on digital rectal examination, prostate-specific antigen (PSA) level and transrectal ultrasonographic findings are not accurate for detection of ECE or SVI [6, 7]. Other imaging-based methods including magnetic resonance imaging (MRI) have demonstrated promising but heterogeneous results with regard to accuracy in local staging with a wide range of reported sensitivities and specificities [3], underlining the need for more precise methods for local staging.

Prostate-specific membrane antigen (PSMA) has recently attracted increased interest as a molecular target for clinical imaging of prostate cancer. PSMA is a type II transmembrane protein that is highly expressed in prostate tissues including benign secretory acinar epithelium, high-grade prostatic intraepithelial neoplasia, and prostate cancer [8]. High levels of PSMA expression have been demonstrated to be significantly associated with tumor stage, high Gleason grade, pre-operative PSA level and a higher risk of biochemical recurrence [9]. ^{68}Ga -labeled PSMA ligands have been introduced for clinical molecular imaging of PSMA expression in prostate cancer [10]. ^{68}Ga -PSMA ligand positron emission tomography/computed tomography (PET/CT) has been shown to be a highly sensitive procedure for image-based restaging of prostate cancer in the context of biochemical recurrence [11–15]. There are several PSMA-targeting radiotracers currently used in clinical routine. The most frequently used tracers are ^{68}Ga -PSMA-HBED-CC and ^{68}Ga -PSMA I&T (imaging and therapy) [10–12]. The intensity of PSMA ligand binding on PET can be quantified using standardized uptake values (SUVs) [11]. A recent study has shown the usefulness of ^{68}Ga -PSMA ligand PET/CT for prediction of lymph node involvement in a cohort of 30 prostate cancer patients prior to radical prostatectomy, but without dedicated assessment of primary tumors [16]. Another study recently evaluated the usefulness of the PSMA ligand ^{68}Ga -PSMA-HBED-CC for localizing cancer in the prostate and surrounding tissue at initial diagnosis on PET/CT [17].

To the best of our knowledge, the performance of ^{68}Ga -PSMA I&T PET/CT for evaluation of local tumor extent, SVI and ECE has not been analyzed in detail before. Therefore, the

aim of the present study was to assess the diagnostic performance of ^{68}Ga -PSMA I&T PET/CT for evaluation of local tumor extent prior to radical prostatectomy. To that end, imaging findings were correlated with final whole-gland histopathology including Gleason grade, T stage, lobe infiltration, ECE, and SVI.

Materials and Methods

Study Population

The study population consisted of 21 patients (mean age 68.1 ± 6.0 years, range 56–77 years) with prostate cancer who underwent a ^{68}Ga -PSMA I&T PET/CT for local staging before either open (20 patients) or laparoscopic (1 patient) radical prostatectomy. Data were retrospectively analyzed in compliance with the regulations for retrospective studies set up by the local Institutional Review Board and in compliance with the principles of the Declaration of Helsinki.

Synthesis of the ^{68}Ga -PSMA Ligand, PET/CT Acquisition and Image Reconstruction

^{68}Ga -PSMA I&T was synthesized as described elsewhere [18]. Patients underwent ^{68}Ga -PSMA I&T PET/CT on a dedicated PET/CT system (Biograph mCT 128 Flow; Siemens, Knoxville, TN) equipped with an extended field-of-view LSO PET component, a 128-slice spiral CT component, and a magnetically driven table optimized for continuous scanning. After intravenous injection of 98 ± 25 MBq (range 60–130 MBq) of the ^{68}Ga -PSMA ligand, image acquisition was started with a low-dose non-enhanced helical CT scan (120 kV, mA-modulated, pitch 1.2, reconstructed axial slice thickness 5.0 mm) performed for attenuation correction of PET data. At 60 min after injection, whole-body PET imaging was performed with continuous bed motion at a speed of 0.9 mm/s for the chest and abdomen and 2.1 mm/s for the legs. All studies were reconstructed using time-of-flight and point-spread function information combined with an iterative algorithm (Ultra HD®; Siemens Healthcare; two iterations, 22 subsets, matrix 200; zoom 1.0; gaussian filter of 5.0).

PET Image Analysis and Quantification

Two board-certified specialists in nuclear medicine and radiology blinded to the results of the histopathological evaluation read all datasets independently and resolved any disagreements by consensus. Fused transaxial ^{68}Ga -PSMA I&T PET/CT images were analyzed. The criterion for prostatic tumor infiltration was: focal or diffuse ^{68}Ga -PSMA ligand accumulation above the intraprostatic background. In addition, tumor infiltration of the prostate was assessed on the

basis of lobes (unilateral vs. bilateral infiltration). The criteria for ECE were: angulated contour of the prostate gland (Fig. 1), or obliteration of the rectoprostatic angle (Fig. 2) [19]. Outside the prostate, pathological ^{68}Ga -PSMA ligand accumulation was identified as tracer uptake exceeding that of background tissue. The number and location of metastases were recorded. Circular regions of interest were drawn around areas with focally increased uptake in transaxial slices, and tracer uptake was quantified in terms of SUVs. For assessment of tumor volumes on ^{68}Ga -PSMA I&T PET/CT, isocontour volumes of interest were used with a SUV threshold of 40% of maximum [20]. SUV_{peak} was obtained using a 1-mL sphere automatically positioned so as to have the greatest mean value. Mean (SUV_{mean}) and maximum SUV (SUV_{max}) were obtained using the isocontour volumes of interest. All ^{68}Ga -PSMA I&T PET/CT images were analyzed on a dedicated workstation equipped with a commercial software package (*syngo*-via; Siemens Healthcare).

Pathological Evaluation

Prostatectomy specimens were fixed in 10% formalin for at least 18 h, and then dye was applied to their surface (black dye on the right side of each specimen, and blue dye on the left). The distal 5-mm portion of the apex and base were removed and examined using the cone method. The remainder of each gland was serially sliced from the apex to the base at intervals of 3–4 mm, and slices were paraffin-embedded as anterior and posterior sections where possible. If the sections were too large, the anterior and posterior slices were cut in half. The seminal vesicles were removed and processed separately. The slices were then fixed for a further 12 h in formalin retained in their respective and numbered cassettes. After paraffin embedding, microslides were placed on glass slides and stained with hematoxylin and eosin.

On pathological analysis, cancer foci were outlined in ink on all slides and a Gleason score was obtained for each cancer focus. All Gleason scores and outlined areas were merged to provide an overall degree of infiltration and a Gleason score for each lobe separately. Staging of the tumors was based on the current UICC guidelines, 7th edition, 2010 [21]. Tumors confined to the prostate were considered stage pT2 with a

refinement according to whether less or more than a half of one lobe or both lobes were infiltrated. Tumors with ECE were assigned stage pT3a and if infiltration of the seminal vesicle was present stage pT3b. Infiltration of the rectum or structures other than the seminal vesicles were required for assignment of stage pT4.

Statistical Analysis

All patient and imaging data from our institutional relational database were evaluated. Continuous variables are expressed as means $\pm$ standard deviation. Categorical variables are presented with absolute and relative frequencies. For between-group comparisons of continuous data, p values were calculated from a two-sided t test. Imaging findings (SUV, PET tumor volume) were correlated with other parameters using a linear regression model. Correlations were analyzed using Pearson's correlation and Spearman's rank correlation with regression lines derived from the linear regression model. A p value of 0.05 was used as the cut-off for statistical significance. Statistical evaluation and illustrations were performed using R statistical software (version 3.0.3) [22].

Results

Patient Characteristics

Relevant patient characteristics are shown in Table 1. The median Gleason score was 7. The mean preoperative PSA level was 11.9 ± 13.0 ng/ml (range 1.3–58.0 ng/ml). Of the 21 patients, 17 (81.0%) had tumor infiltration of both prostate lobes, and 4 (19.0%) had unilateral involvement. Five of the 21 patients had positive surgical margins and ten had ECE (pT stage $\geq 3a$) on histopathological work-up. SVI was found in four patients (19.0%).

Diagnostic Performance of ^{68}Ga -PSMA I&T PET/CT

On ^{68}Ga -PSMA I&T PET/CT, obliteration of the rectoprostatic angle was seen in seven patients (33.3%), and an angulated contour of the prostate gland was seen in

Fig. 1 ^{68}Ga -PSMA I&T PET/CT images in a 62-year-old patient. **a** Transaxial CT image of the prostate. **b** The PET/CT image shows intense tracer accumulation (SUV_{peak} 19.1, SUV_{max} 42.9, SUV_{mean} 2.8) in the

primary and an angulated contour of the prostate gland (arrows), consistent with extracapsular extension

Fig. 2 ^{68}Ga -PSMA I&T PET/CT images in a 77-year-old patient. **a** Transaxial CT image of the prostate. **b** The PET/CT image shows intense tracer accumulation (SUV_{peak} 12.9, SUV_{max} 24.9, SUV_{mean} 15) in the

primary and obliteration of the rectoprostatic angle (*arrow*), consistent with extracapsular extension

ten patients (47.6%). Sensitivity, specificity, positive predictive value and negative predictive value were 94.7%, 75.0%, 97.3% and 60.0% for tumor infiltration of an individual prostate lobe, 75.0%, 100.0%, 100.0% and 97.4% for SVI, 90.0%, 90.9%, 90.0% and 90.9% for ECE using an angulated contour of the prostate as the criterion, and 60.0%, 90.9%, 85.7% and 71.4% for ECE using obliteration of the rectoprostatic angle as the criterion. Example ^{68}Ga -PSMA I&T PET/CT images of primary tumors, ECE and SVI are shown in Figs. 1, 2, 3, and 4.

^{68}Ga -PSMA I&T PET/CT Findings and Their Relationship with Other Parameters

Data on tracer uptake in primary tumors are shown in Table 2. The intraprostatic SUV_{peak} of primary tumors was positively correlated with preoperative PSA values ($r_p = 0.44$, $p = 0.047$). SUV_{peak} was significantly positively correlated with Gleason score ($r_s = 0.49$, $p = 0.025$). SUV_{peak} was significantly higher in patients with ECE than in those with organ-confined tumors (15.7 ± 11.6 vs. 5.5 ± 2.6 , $p = 0.010$; Fig. 5). In addition, both SUV_{max} and SUV_{mean} were significantly higher in patients with ECE ($p = 0.039$ and 0.029 , respectively). However, SUV_{peak} , SUV_{max} and SUV_{mean} were not significantly higher in patients with SVI than in those without (11.7 ± 5.7 vs. 10.1 ± 10.4 , 20.7 ± 17.1 vs. 15.7 ± 15.4 and 11.5 ± 9.2 vs. 9.0 ± 8.9 , respectively; $p = 0.763$, 0.574 and 0.622 , respectively).

The mean prostate volume was $48.1 \pm 16.9 \text{ cm}^3$ (range 19.0 – 80.0 cm^3). The mean intraprostatic histopathological tumor volume was $9.0 \pm 7.6 \text{ cm}^3$ (range 1.9 – 28.9 cm^3). The mean tumor volume estimated from ^{68}Ga -PSMA I&T PET/CT was $4.6 \pm 5.5 \text{ cm}^3$ (range 0.9 – 25.2 cm^3). There was a significant correlation between tumor volume on histopathological evaluation and tumor volume estimated from ^{68}Ga -PSMA I&T PET/CT ($r_p = 0.45$, $p = 0.039$) and also between preoperative PSA values and tumor volume derived from ^{68}Ga -PSMA I&T PET/CT ($r_p = 0.75$, $p < 0.001$; Figs. 6 and 7). Preoperative PSA values showed a significant correlation with tumor volume on histopathological evaluation ($r_s = 0.68$, $p < 0.001$).

Discussion

^{68}Ga -PSMA ligand PET/CT has recently gained prominence as a highly sensitive means for restaging of prostate cancer in

Table 1 Characteristics of 21 patients who underwent ^{68}Ga -PSMA I&T PET/CT prior to radical prostatectomy for adenocarcinoma of the prostate

Characteristic	Value
Age (years), median (range)	68 (56–77)
Therapy, n (%)	
Radical prostatovesiculectomy	20
Extraperitoneal endoscopic radical prostatovesiculectomy	1
Initial PSA (ng/dL), mean, SD	11.9
Prostate volume (cm^3), mean $\pm$ SD	48.1 ± 16.9
T stage, n (%)	
2a	0 (0.0)
2b	2 (9.5)
2c	9 (42.9)
3a	6 (28.6)
3b	4 (19.0)
4	0 (0.0)
N+	2 (9.5)
R1	5 (23.8)
Gleason score, n (%)	
6	2 (9.5)
7a (3 + 4)	10 (47.6)
7b (4 + 3)	4 (19.0)
8	3 (14.3)
9	2 (9.5)
10	0 (0.0)
Tumor extent, n (%)	
Unilateral	4 (19.0)
Bilateral	17 (81.0)
Seminal vesicle invasion, n (%)	
None	17 (81.0)
Unilateral	4 (19.0)
Bilateral	0 (0.0)

PSA prostate-specific antigen, R+ positive surgical margins, N1 tumor positive lymph nodes.

Fig. 3 ^{68}Ga -PSMA I&T PET/CT images in a 62-year-old patient. **a, b** Transaxial CT images of the prostate (**a**) and at the level of seminal vesicles (**b**). **c, d** The PET/CT images show intense tracer accumulation (SUV_{peak} 9.4, SUV_{max} 14.6, SUV_{mean} 9.0) in the primary (**c**) and extension of the tumor to the prostate base with SVI (**d**) on the left side

the setting of biochemical recurrence after primary therapy for prostate cancer [10–12]. In a pilot study on 21 patients, we assessed the value of ^{68}Ga -PSMA I&T PET/CT for local staging of primary tumors. Our results suggest a potential role for ^{68}Ga -PSMA I&T PET/CT if and which nerve-sparing surgery approach to apply. The rates of urinary incontinence and erectile dysfunction after radical prostatectomy are known to markedly depend on whether a bilateral or unilateral nerve-sparing surgical technique is chosen [2]. With the current shift towards younger age at initial diagnosis, salvaging sexual function has become a more prominent issue which should be discussed in the light of novel preoperative imaging modalities. In order to ensure oncological control, patients must be well informed that sacrificing the neurovascular bundle may be inevitable. According to the current European guidelines on prostate cancer, contraindications to nerve-sparing surgery are clinical stage $>\text{cT2c}$ or cT3 , Gleason score >7 , or more than one biopsy with a Gleason score >6 at the side

of nerve preservation. Nerve-sparing surgery may be offered to potent patients with a low risk for extracapsular cancer (T1c, Gleason score <7 and PSA <10 ng/mL).

In prostate needle biopsy, the percentage of cancerous tissue is associated with tumor ECE, as well as positive surgical margins and SVI [23]. However, these findings were obtained from systematic needle core biopsies. While it may be valid to make assumptions about tumor extent from systematic biopsies, this may be less appropriate in patients with imaging-guided biopsies. Random biopsies are still indicated in the diagnosis of prostate cancer [24], but current practice includes a growing number of patients with MRI fusion or computerized transrectal ultrasound-guided biopsies with artificial neural network analysis [25, 26]. The choice of nerve-sparing approach may be facilitated using multiparametric MRI in patients with intermediate-risk or high-risk prostate cancer (level of evidence 2b). Also, intraoperative frozen-section analysis may guide the decision on nerve preservation [24]. Using established criteria originally derived from MRI, i.e. obliteration of the rectoprostatic angle and angulated contour of the prostate gland, ^{68}Ga -PSMA I&T PET sensitivity identified ECE, suggesting a potentially valuable role for local staging. Although these PET criteria, which were originally observed on MRI, were adapted to the specific situation of PET, they provided reliable identification of ECE. An angulated contour of the prostate gland was the most reliable PET criterion for prediction of ECE, yielding a sensitivity of 90%. Our results support the use of ^{68}Ga -PSMA I&T PET/CT prior to surgery as particularly helpful with regard to treatment planning for two additional reasons: intraprostatic SUV was highly correlated with the presence of ECE, and also ^{68}Ga -PSMA I&T PET/CT was able to identify cancerous lesions of low Gleason grade inside the prostate lobe, thereby providing valuable data for choosing the right side and extent for nerve preservation. MRI provided poorer results in previous studies, especially when trying to identify patterns with Gleason score <7 inside the prostate gland [27].

Fig. 4 ^{68}Ga -PSMA I&T PET/CT images in a 55-year-old patient. **a, b** Transaxial CT images of the prostate (**a**) and at the level of seminal vesicles (**b**). **c, d** The PET/CT images show intense tracer accumulation (SUV_{peak} 34.2, SUV_{max} 46.5, SUV_{mean} 30.0) in the primary extending into both prostate lobes (**c**) and absence of SVI (**d**)

Table 2 Semiquantitative evaluation of ^{68}Ga -PSMA I&T PET/CT in organ-confined tumors and tumors with extracapsular extension

Parameter	Organ-confined disease	Extracapsular extension	<i>p</i> value	Total
SUV_{peak}				
Mean $\pm$ SD	5.5 $\pm$ 2.6	15.7 $\pm$ 11.6	0.010*	10.4 $\pm$ 9.5
Range	2.8–11.2	3.2–34.2		2.8–34.2
SUV_{max}				
Mean $\pm$ SD	10.2 $\pm$ 5.6	23.8 $\pm$ 19.6	0.039*	16.6 $\pm$ 15.4
Range	4.1–22.2	4.3–60.3		4.1–60.3
SUV_{mean}				
Mean $\pm$ SD	5.6 $\pm$ 3.2	13.8 $\pm$ 11.0	0.029*	9.5 $\pm$ 8.8
Range	2.5–13.7	2.5–31.9		2.5–31.9

* $p < 0.05$

We sought to determine in particular whether ^{68}Ga -PSMA I&T PET/CT is able to predict SVI prior to surgery. It is well known that the presence of SVI is an important factor in patient prognosis [5]. The presence of SVI is predictive of local recurrence and metastatic disease during long-term follow-up. Targeted biopsy of the seminal vesicles is currently not a diagnostic standard procedure. Patients with a positive biopsy at the base of the prostate, clinical stage $>\text{T2b}$ or PSA >10 ng/mL may be selected for biopsy of the seminal vesicles [28, 29]. Preparation of the seminal vesicles poses a surgical challenge during radical prostatectomy. While complete resection of a seminal vesicle may increase local oncological control, sparing the distal tip may benefit nerve sparing because the pelvic nerve bundle with its sensory and motor branches is typically located around 3–10 mm caudally from the top of the seminal vesicle

[30]. In our study, ^{68}Ga -PSMA I&T PET/CT had a sensitivity of 75.0% and a specificity of 100.0% for detection of SVI, although these results have to be regarded with caution due to the relatively low number of patients with SVI (four patients) evaluated by PET in this study. Future larger studies with a higher number of SVI-positive patients will shed further light on the precise value of PET for detection of SVI, particularly in comparison to MRI, which has shown heterogeneous results for prediction of seminal vesicle involvement [3].

We observed a significant correlation between tumor volume on histopathological evaluation and tumor volume estimated from ^{68}Ga -PSMA I&T PET/CT ($r_p = 0.45$, $p = 0.039$), indicating that PET/CT may also be a predictor of intraprostatic tumor mass. PSA has been shown to be significantly associated with tumor volume in small, medium and

Fig. 5 SUV_{peak} of primary prostate gland organ-confined tumors ($<\text{pT3a}$, *left*) and tumors with extracapsular extension ($\geq\text{pT3a}$, *right*) on histopathological evaluation ($p = 0.010$). Individual data points with means and standard deviations are shown

Fig. 6 Correlation between histopathological tumor volume with tumor volume calculated from ^{68}Ga -PSMA I&T PET/CT showing the regression line ($r_p = 0.45$, $p = 0.039$); black extracapsular extension (ECE), white organ confined disease)

large prostates [31]. In this study, preoperative PSA was also significantly associated with tumor volume on histopathological evaluation. However, the correlation was more robust for tumor volume derived from ^{68}Ga -PSMA I&T PET/CT ($r_s = 0.68$ vs. $r_s = 0.75$). A recently published study evaluated the usefulness of the PSMA ligand ^{68}Ga -PSMA-HBED-CC for localizing cancer in the prostate and surrounding tissue at

initial diagnosis on PET/CT [17]. Using another radiotracer, the authors found that PET/CT correctly detected invasion of the seminal vesicles (in 11 of 21 patients, 52%) with 73% sensitivity, and tumor spread through the capsule (in 12 patients, 57%) with 50% sensitivity. Our study using the radiotracer ^{68}Ga -PSMA I&T showed some more promising results, demonstrating a sensitivity of 75.0% for detection of SVI and 90.0% for ECE. In another study of ^{18}F -fluorocholine dynamic time-of-flight PET/MR imaging in newly diagnosed intermediate-risk to high-risk prostate cancer, Choi et al. found that combined PET and MR imaging showed improved sensitivity (88%) for prediction of pathological ECE compared with MR imaging (50%) and PET (75%) performed separately [32]. Given the limitations of choline derivatives for PET/CT of prostate cancer, a direct comparison between multiparametric MRI and ^{68}Ga -PSMA I&T PET/CT for evaluation of tumor extent, ECE and SVI would be interesting in future studies, but was not performed in this pilot study.

This study had some limitations. All patients in this study underwent a ^{68}Ga -PSMA I&T PET/CT scan after core needle biopsy and confirmation of prostate cancer prior to radical prostatectomy. Therefore, the ^{68}Ga -PSMA I&T PET/CT findings had no influence on the decision for biopsy in this setting, or biopsy targeting. A direct correlation between our ^{68}Ga -PSMA I&T PET/CT and histopathological data with MRI imaging was not possible because the patients did not systematically undergo MRI prior to surgery in this study. Still, the very prominent correlation between ^{68}Ga -PSMA I&T PET/CT-derived intraprostatic SUV and positive tumor histology

Fig. 7 The upper hatched bars show serum PSA values in increasing order prior to surgery in all patients. The lower bars show the corresponding tumor volumes derived from ^{68}Ga -PSMA I&T PET/CT (black bars) in cm^3 ($r_p = 0.75$, $p < 0.001$) and the histopathological tumor volume (gray bars; $r_s = 0.68$, $p < 0.001$)

be the foundation for further investigations. To that end, ^{68}Ga -PSMA I&T PET/CT may potentially be used for image fusion-guided biopsy in the future which, according to our results, may be of special interest for the detection of prostate cancer with low Gleason grades. Previous studies have shown that the specificity of PET imaging-guided biopsy is suboptimal. However, these initial studies of PET-guided biopsy involved the use of older tracers such as ^{11}C -acetate and ^{11}C -choline, which have become more or less obsolete in the era of ^{68}Ga -PSMA I&T PET discussed here [33].

The usefulness of combined MRI and ^{68}Ga -PSMA I&T PET/CT for prostate biopsy is currently being investigated [34], but there are still very few data on the correlation between MRI plus ^{68}Ga -PSMA I&T PET/CT and biopsy histology and whole-gland histology after prostatectomy. Finally, we used an SUV threshold of 40% of maximum for calculation of tumor volume on PET. Although this approach has been widely used in PET studies using ^{18}F -FDG as radiotracer [20], it may not be the optimal cut-off for ^{68}Ga -PSMA I&T. However, tumor volume on histopathological evaluation and tumor volume estimated from ^{68}Ga -PSMA I&T PET/CT were significantly correlated confirming that the threshold applied in this study provided useful tumor delineation.

Conclusion

^{68}Ga -PSMA I&T PET/CT prior to radical prostatectomy can contribute to presurgical local staging of prostate cancer. In this pilot study, we observed promising results for prediction of lobe infiltration, ECE and SVI, providing a rationale for larger prospective studies.

Compliance with Ethical Standards

Conflict of Interest Hans-Jürgen Wester is shareholder of Scintomics. Christoph-Alexander Joachim von Klot, Axel Stuard Merseburger, Sebastian Schmuck, Frank Michael Bengel, Markus Antonius Kuczyk, Christoph Henkenberens, Hans Christiansen, Wiebke Solass, Marcel Lafos and Thorsten Derlin declare no conflict of interest. No funding was received.

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patient data was anonymized prior to statistical analysis. No additional data were created nor used aside from the retrospective evaluation of our database.

Informed Consent The institutional review board of our institution approved this retrospective study, and the requirement to obtain informed consent was waived.

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