
The Impact of Peptide Amount on Tumor Uptake to Assess PSMA Receptor Saturation on ^{68}Ga -PSMA-11 PET/CT in Patients with Primary Prostate Cancer

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^{68}Ga -labeled prostate-specific membrane antigen (PSMA) is often produced on-site, where usually a fixed amount of peptide is conjugated to the generator eluate. However, fluctuations in specific activity might influence tracer distribution and tumor accumulation. Therefore, our aim was to investigate the potential effect of varying the administered peptide amount on ^{68}Ga -PSMA-11 uptake in tumors using PET/CT in patients with primary prostate cancer (PCa). Additionally, the impact of tumor volume on this potential effect and on accumulation in reference organs was assessed. **Methods:** The imaging data of 362 men with primary PCa who underwent ^{68}Ga -PSMA-11 PET/CT were retrospectively included. Scans were quantified for normal tissue and primary tumors. Patients were divided into 3 groups based on their tumor volume. Correlation and multivariable linear regression analyses were performed. **Results:** The median index lesion volume was 9.50 cm^3 (range, $0.064\text{--}174\text{ cm}^3$). Groups were based on quartiles of prostatic lesion volume: $\leq 4.11\text{ cm}^3$ (group 1), $4.11\text{--}20.6\text{ cm}^3$ (group 2), and $\geq 20.6\text{ cm}^3$ (group 3). No correlation was found between administered peptide amount and tumor uptake (SUV_{mean} or SUV_{peak}) for any group, except for a significant correlation for SUV_{mean} in the first group ($P = 0.008$). Linear regression analysis supported these findings. **Conclusion:** The amount of administered peptide had no evident effect on ^{68}Ga -PSMA-11 uptake in tumors, except for a significant positive correlation between administered peptide amount and tumor SUV_{mean} for group 1. The findings imply that no receptor saturation occurs in men with primary PCa at peptide levels of about $2.5\text{ }\mu\text{g}$.

Key Words: PSMA; prostate cancer; peptide amount; receptor saturation; specific activity

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Prostate-specific membrane antigen (PSMA) ligands target the PSMA receptor, which is significantly overexpressed on the surface of prostate cancer (PCa) cells (*1*). Radiolabeled PSMA-directed ligands are increasingly used for both diagnosis and therapy in PSMA-positive PCa. The first clinical PSMA-directed tracer, ^{68}Ga -labeled PSMA, is a highly tumor-specific biomarker that is used

today for diagnosis and staging of both primary and metastatic or oligometastatic PCa (*2–4*). The commercial availability of $^{68}\text{Ge}/^{68}\text{Ga}$ generators and PSMA ligands has ensured that this development is now firmly embedded in many clinics.

The on-site labeling procedure for ^{68}Ga -PSMA-11 involves conjugation of a usually fixed amount of peptide to the generator eluate, since whole vials that hold a fixed amount PSMA peptide are generally used during labeling procedures. The administered amount of radioactivity is often standardized between patients to ensure comparable inter- and inpatient image quality. However, radioactivity levels in the $^{68}\text{Ge}/^{68}\text{Ga}$ generator decrease over its lifetime, resulting in variable elution efficiencies, whereas the amount of peptide added to this generator eluate is kept constant. Because patients receive approximately equal radioactivity doses, total peptide amounts per injection will vary. In receptor-based imaging and therapy, inconstant specific activities can lead to altered tumor accumulation profiles due to varying levels of receptor occupancy in target and nontarget tissues. Though this effect has been demonstrated before in pharmacokinetic models for therapeutic doses of ^{90}Y -labeled DOTATATE (*5*) and in clinical cases for ^{89}Zr -labeled antibodies (*6*), it has not yet been demonstrated for ^{68}Ga -PSMA-11.

Previously, our group showed variable ^{68}Ga -PSMA-11 uptake profiles in primary PCa lesions using dynamic PET/CT in a small population of men with localized PCa (*7*). It was hypothesized that this might be explained by different receptor saturation states of intraprostatic PCa lesions. After all, an uptake plateau could correspond to a small tumor that has a limited total receptor amount and thus reaches the total occupancy of available receptors, whereas such a total occupancy of receptors will probably not occur in larger tumors or in metastatic or oligometastatic PCa that tends to have a larger amount of PSMA receptors. The presence of tumor receptor saturation may potentially be relevant in PSMA-based radionuclide therapy, as usually much larger peptide amounts are administered (e.g., $\sim 250\text{ }\mu\text{g}$ using ^{177}Lu -PSMA) than in imaging with ^{68}Ga -PSMA-11 ($\sim 5\text{ }\mu\text{g}$). In addition, interpatient variability in administered ^{68}Ga -PSMA-11 peptide amounts could lead to differences in tumor and organ distribution if receptor saturation were to take place.

For this reason, there is an urgent need to define whether receptor saturation occurs in ^{68}Ga -PSMA-11 distribution in primary PCa and whether this occurrence is dependent on lesion volume. Our research aims were to assess these uncertainties by quantitatively investigating the potential effect of varying administered peptide amounts on ^{68}Ga -PSMA-11 uptake in tumor lesions using PET/CT in patients with primary PCa and to assess the impact of tumor

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volume on this potential effect and on accumulation in reference tissue.

MATERIALS AND METHODS

Study Population

This retrospective data analysis study was approved by the Institutional Review Board (IRBd20-201) of The Netherlands Cancer Institute. All patients had given informed consent for use of data clinically obtained during routine care via institutional procedures. Data on men with intermediate- or high-risk (\geq cT3, Gleason score \geq 7, or prostate-specific antigen \geq 20 ng/mL) primary PCa who underwent ^{68}Ga -PSMA-11 PET/CT before treatment between January 2016 and May 2020 were included. Patients were excluded from analysis if no PSMA-positive lesion was visualized on ^{68}Ga -PSMA-11 PET/CT (defined as no intraprostatic accumulation higher than prostate background). Patients did not receive any hormone therapy before their scan.

Image Acquisition and Analysis

^{68}Ga -Glu-urea-Lys(Ahx)-HBED-CC (^{68}Ga -PSMA-11) was produced in-house using a fully automated system (Scintomics GmbH) by combining 10 μg of PSMA-11 with the generator eluate. Patients were prepared and images acquired according to standard clinical protocols. An intravenous bolus of approximately 100 MBq (2016 until September 2019) or approximately 150 MBq (from September 2019 onward) of ^{68}Ga -PSMA-11 was injected approximately 60 min before the start of the scan. Whole-body (mid thigh to skull base) scans were acquired on a Gemini TF, Gemini TF BigBore, or Vereos digital PET/CT system (Philips) using harmonized scan and reconstruction protocols (4×4 mm voxel sizes). In addition, a low-dose CT scan was acquired for attenuation correction and anatomic correlation.

Quantitative evaluations of imaging data were performed using 3D Slicer (slicer.org, version 4.11) (8). Since there is no gold standard for prostate tumor segmentation on PSMA PET, 2 segmentation methods (i.e., standardized manual vs. threshold-based) were compared. On the basis of these results, provided in the supplemental materials (available at <http://jnm.snmjournals.org>), further analysis was performed by standardized manual segmentation of all lesions on PET/CT. Mean absolute uptake (MBq/cm³), SUV_{mean}, and SUV_{peak} were used to express ^{68}Ga -PSMA-11 uptake. SUV_{peak} was defined as the 1 cm³ that showed the highest activity concentration within the volumes of interest.

In all scans, spheric volumes of interest of 2.0 cm diameter were drawn to obtain normal-tissue uptake in the parotid gland, aortic arch, liver (diameter, 5.0 cm), kidney cortex, and gluteal muscle. Normal-tissue SUV_{mean} and SUV_{peak} were normalized to the uptake in the aortic arch (referred to as blood pool), and these ratios were then compared among patient groups. In cases of multifocal intraprostatic disease, both lesions were segmented, but the most profound or largest lesion (referred to as the index lesion) was used for initial analysis.

Statistical Analysis

Statistical analyses were performed in R (version 3.6.3) (9). Patients were categorized into 3 quartile (Q) groups based on index lesion volume (group 1: \leq Q1, group 2: Q1 to Q3, and group 3: \geq Q3). Differences in patient characteristics among these groups were evaluated using ANOVA or, in cases of nonnormal distribution, a Kruskal–Wallis test with Bonferroni adjustments to account for multiple testing. Spearman correlation coefficient tests were performed to investigate potential associations between administered PSMA peptide amount and observed organ and tumor uptake on PET per group. A linear regression analysis was performed to assess a potential interaction effect between administered peptide amount and index lesion volume on ^{68}Ga -PSMA-11 tumor uptake. In addition, a multivariable regression analysis was performed to identify other potential variables that impact ^{68}Ga -PSMA-11 tumor uptake

and, thus, could complicate interpretation and comparison of the results among groups. Parameters that were tested as covariates were age, body mass index, estimated glomerular filtration rate, injection-to-acquisition interval, scanner type, furosemide administration during scan, risk of PCa recurrence, and disease spread. Risk of PCa recurrence was based on the D'Amico risk classification (10). The spread of disease, and thus also the presence or absence of metastases, was categorized into 4 groups: local, locally advanced, oligometastatic, and metastatic. The definition of locally advanced was staging with either T3 or T4, or with N1 independent of T (11). Oligometastatic disease was defined as no more than 5 metastatic tumors, excluding 4 or fewer synchronous pelvic lymph nodes (12,13). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Initially, 391 patients were retrieved for inclusion. Of these, 29 were excluded from further analysis: 15 because no PSMA-positive tumor was detected and 14 because the PET or CT scan was missing. Finally, imaging data from 362 men with PCa were used for analysis. The median injected activity was 98.7 MBq (range, 71.2–184 MBq) over the entire population, with a median total administered peptide amount of 2.49 μg (range, 1.06–5.91 μg). Furosemide (10 mg) was administered to 71.5% of the patients, and iodinated contrast medium was used in none of the cases. The median volume of the prostatic index lesions was 9.50 cm³, with an interquartile range of 4.11–20.6 cm³; the 3 groups were therefore defined as \leq 4.11 cm³ (group 1), 4.11–20.6 cm³ (group 2), and \geq 20.6 cm³ (group 3). Patient characteristics and demographics over the 3 groups are shown in Table 1.

For parotid, liver, and gluteus, no significant differences in tissue-to-blood ratios were observed for either SUV_{mean} or SUV_{peak} over the groups. However, the kidney-to-blood ratio of group 3 was significantly lower than that of group 1 for SUV_{mean} and SUV_{peak}, though the absolute differences between the groups were quite small. The results are shown in Figure 1. Median SUV_{mean} and SUV_{peak} for index lesions were 5.09 (range, 1.39–15.9) and 7.53 (range, 2.19–44.7) over all patients, respectively. However, 71 patients had more than 1 PCa lesion, and when taking into account all PCa lesions, median SUV_{mean} and SUV_{peak} were 4.78 (range, 1.39–15.9) and 7.54 (range, 2.19–44.7), respectively. Index lesion volume correlated with lesion SUV_{mean} and SUV_{peak} (both *P* < 0.001; Supplemental Fig. 1), and accordingly, tumor SUV_{mean} and SUV_{peak} significantly differed between the patient groups as is shown in Figure 2.

Uptake vs. PSMA Peptide Amount

The effect of administered peptide amount on ^{68}Ga -PSMA-11 tumor uptake per group was assessed using correlation plots and an interaction linear regression model. The results of Spearman correlation, based on index lesions only, are presented in Figure 3. No significant correlation between peptide amount and lesion SUV_{mean} or SUV_{peak} was observed, except for a significant positive low correlation (*P* = 0.008) for SUV_{mean} in patients with small index lesion volumes (group 1). Similar results were observed while taking into account all PCa lesions (Supplemental Fig. 2). In addition, potential correlations of administered peptide amount on organ uptake per group were assessed (Supplemental Fig. 3).

Linear regression model results confirmed these findings and showed that, for both SUV_{mean} and SUV_{peak}, there was no interaction effect between administered peptide amount and tumor volume. In other words, the effect of administered peptide amount on

TABLE 1
Patient Demographics and Characteristics for Patients Receiving ⁶⁸Ga-PSMA-11 per Group Based on Lesion Volume

Characteristic	Group 1	Group 2	Group 3	P
<i>n</i>	91	180	91	
Age (y)	67 ± 6	69 ± 7	68 ± 8	0.044
Body mass index (kg/m ²)	26.6 ± 3.50	26.0 ± 3.30	26.8 ± 3.81	0.151
eGFR (mL/min/1.73 m ²)	76.6 ± 13.1	76.5 ± 16.1	76.5 ± 20.8	0.999
Injection-to-acquisition interval (min)	58 ± 11	59 ± 11	60 ± 9	0.379
Administered peptide amount (μg)	2.83 ± 0.88	2.58 ± 0.76	2.52 ± 0.66	0.015
Injected radioactivity (MBq)	111.0 ± 24.9	101.1 ± 17.9	98.6 ± 11.0	<0.001
Furosemide during scan	51 (56%)	138 (77%)	70 (77%)	0.001
Scanner type				<0.001
Gemini TF Big Bore	37 (41%)	92 (51%)	55 (60%)	
Gemini TF	21 (23%)	56 (31%)	25 (28%)	
Vereos PET/CT	33 (36%)	32 (18%)	11 (12%)	
Risk of recurrence				<0.001
Intermediate	35 (39%)	22 (12%)	3 (3%)	
High	56 (61%)	158 (87%)	88 (97%)	
Disease spread				<0.001
Local	64 (70%)	71 (39%)	9 (10%)	
Locally advanced	26 (29%)	82 (46%)	45 (50%)	
Oligometastatic	1 (1%)	24 (13%)	28 (31%)	
Metastatic	0 (0%)	3 (2%)	9 (10%)	

eGFR = estimated glomerular filtration rate.

Group 1 is ≤4.11 cm³ (≤Q1), group 2 is 4.11–20.6 cm³, and group 3 is ≥20.6 cm³ (≥Q3). Continuous variables are shown as mean ± SD; categorical variables are shown as number and percentage.

the SUV_{mean} and SUV_{peak} of tumors was not modified by tumor volume. On the basis of these results, receptor saturation was not deemed likely to occur in any of the groups or, thus, in patients with low tumor volumes, as hypothesized.

For the multivariable analysis, SUVs were log-transformed to correct for the nonnormal distribution. The results of this multivariable analysis showed that, after exclusion of variables that appeared not significant, the variable “body mass index” had a significant positive impact on both SUV_{mean} (*P* = 0.0123) and SUV_{peak} (*P* = 0.0300). Variables such as age, estimated glomerular filtration rate, injection-to-acquisition interval, furosemide administration during scan, type of scanner, risk of PCa recurrence, and disease spread did not prove relevant.

DISCUSSION

This study assessed the effect of peptide amount and index lesion volume on ⁶⁸Ga-PSMA-11 uptake on PET/CT in 362 primary PCa patients. Analyses showed that a larger lesion volume was indeed related to a higher tumor uptake on ⁶⁸Ga-PSMA-11 PET/CT, whereas the administered peptide amount did not show such an evident relation. In addition, a linear regression analysis demonstrated no interaction effect between administered peptide amount and lesion volume on tumor uptake (SUV_{mean} and SUV_{peak}), meaning that index lesion volume did not modify the effect of administered peptide amount on tumor uptake. Though these results were

calculated for index lesions only, the outcomes did not change when all lesions per patient were considered in the correlation analysis (Supplemental Fig. 2). Differences in index lesion volume also did not result in relevant variations in normal-tissue accumulation (organ-to-blood ratios for parotid, liver, or gluteal muscle), except for kidney uptake.

The group with the smallest index lesions (volume of ≤4.11 cm³) did reveal a significant positive low correlation between peptide amount and SUV_{mean}; however, this finding did not imply receptor saturation. In fact, if receptor saturation had played any role, a negative correlation would have been hypothesized since smaller tumors are assumed to have fewer receptors and, hence, less capability to bind the ⁶⁸Ga-PSMA-11. Therefore, it was concluded that receptor saturation did not occur in our population with primary disease (<174 cm³ index lesion volume) at peptide amounts between 1.06 and 5.91 μg. Substantial uptake differences might not have been expected beforehand, because of low peptide amounts with relatively small ranges in cases of ⁶⁸Ga-PSMA-11 administration. Labeling with ¹⁸F would possibly result in even greater ranges in administered peptide amounts, since its longer half-life enables use over longer periods after production. Recently, preclinical analyses have been performed regarding such ¹⁸F-labeled PSMA ligands to assess potential effects of administered peptide amounts on accumulation in tumors and organs (14,15). In those studies, both with approximately 100-fold differences in administered molar activities, lower injected molar activities resulted in reduced uptake in PSMA-expressing tissues.

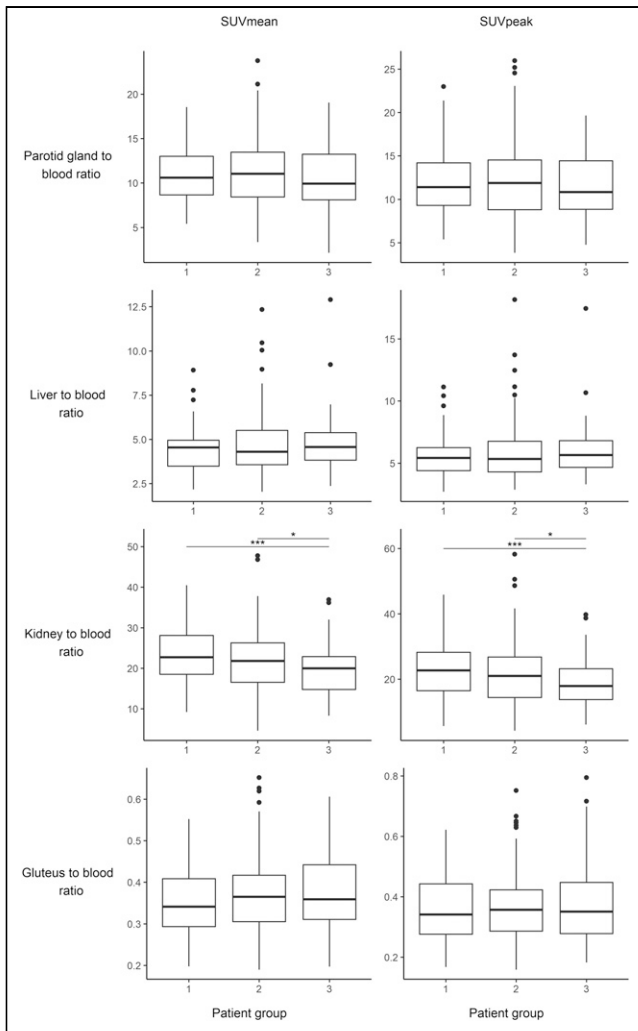


FIGURE 1. Ratios of normal tissue vs. blood (SUV_{mean} and SUV_{peak}) for ^{68}Ga -PSMA-11 per patient group (based on volume of prostatic index lesion: $\leq 4.11\text{ cm}^3$ ($\leq Q1$) (1), $4.11\text{--}20.6\text{ cm}^3$ (2), and $\geq 20.6\text{ cm}^3$ ($\geq Q3$) (3)). $*P < 0.05$. $***P < 0.001$.

Unfortunately, direct translation of these results to the clinical setting remains challenging. In PSMA-based radionuclide therapy, the peptide amounts can easily be 50 times higher than for diagnostic

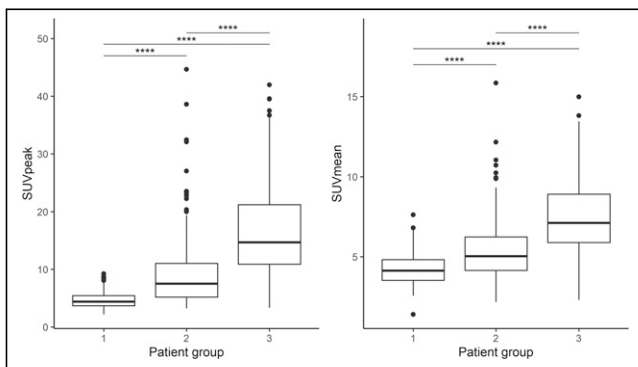


FIGURE 2. Box plots of tumor ^{68}Ga -PSMA-11 uptake per patient group (based on volume of prostatic index lesion: $\leq 4.11\text{ cm}^3$ ($\leq Q1$) (1), $4.11\text{--}20.6\text{ cm}^3$ (2), and $\geq 20.6\text{ cm}^3$ ($\geq Q3$) (3)). $****P < 0.0001$.

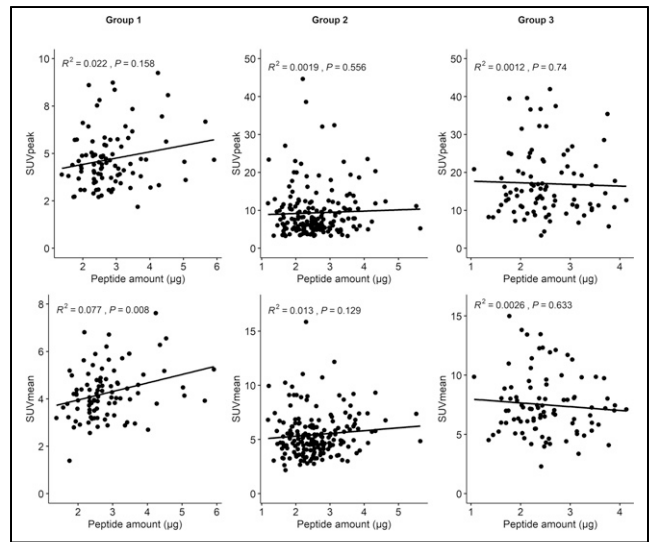


FIGURE 3. Correlation plots of tumor SUV_{peak} or SUV_{mean} vs. administered peptide amount (μg) per patient group (based on volume of prostatic index lesion: $\leq 4.11\text{ cm}^3$ ($\leq Q1$) (1), $4.11\text{--}20.6\text{ cm}^3$ (2), and $\geq 20.6\text{ cm}^3$ ($\geq Q3$) (3)).

imaging; in the metastatic setting also, tumor volumes can be far more profound than those in the current study. Extrapolation of the current results to these settings is difficult, but there nevertheless are some studies that underline the relevance of peptide amounts in these settings (16,17). Still, our results regarding ^{68}Ga -PSMA-11 remain important since no occurrence of receptor saturation in the diagnostic setting was confirmed.

The evaluations of ^{68}Ga -PSMA-11 accumulation in normal tissues showed that groups 1 and 2 had a significantly higher kidney-to-blood ratio than group 3 for SUV_{mean} and SUV_{peak} . It is hypothesized that the higher tumor uptake with increasing lesion size resulted in a lower kidney uptake or renal excretion. Such a tumor sink effect was indeed previously described for ^{68}Ga -PSMA-11, although these studies included PCa patients with much larger tumor volumes (18,19). In these studies, a tumor sink effect was also observed for organs other than kidney, such as salivary glands, spleen, and liver, whereas such was not the case in this study. Probably, tumor volumes were too low in these primary PCa patients to achieve a decrease in normal-tissue uptake. Future research is needed to evaluate these observations for ^{177}Lu -PSMA also. However, for therapy with ^{177}Lu -PSMA I&T in metastatic castration-resistant PCa patients, a simulation study by Begum et al. showed that increasing total tumor volumes (up to $3,000\text{ cm}^3$) resulted in a decrease in tumor and organ uptake (kidney, parotid glands, and submandibular glands) (17).

In the current study, definition of PSMA-positive tumor lesion volume within the prostate was one of the important challenges. Though the use of 2 different strategies has been presented in the supplemental materials, only the manual instead of semiautomatic segmentation was chosen to quantify uptake in tumors. For lesions with relatively low SUVs, segmentation thresholds were set at an SUV of approximately 1, resulting in volumes that consisted of benign prostate as well as tumor tissue. Compared with manual segmentation, these automatically generated volumes overestimated the actual tumor volume, a finding that has been addressed before by other groups (20). Manual segmentation, on the other hand, is inherently observer-dependent but did result in a rather good Dice similarity coefficient of 0.73 (21).

All patients were categorized into 3 groups based on their intraprostatic lesion volume to assess its relation to peptide amount. Some patient characteristics significantly differed among those groups, such as age, administered peptide amount, administered radioactivity, scanner type, risk of recurrence, and disease spread (Table 1). It was hypothesized that the higher age and classification observed with increasing lesion volume can be explained by the larger and thus more aggressive tumors (22). Such a similar trend of higher Gleason score and increasing age resulting in higher tumor loads was previously described by Gaertner et al. (19). For administered peptide amount, the analyses focused on a trend within ranges of this peptide amount instead of the mean differences among groups, and therefore, this significant difference among groups probably did not cause any bias. Differences in administered radioactivity were also considered, since SUV measures inherently correct for injected activity and patient weight. Though these significant variables were not likely to impact the conclusions, a multivariable analysis was performed to assess whether these individual parameters potentially could impact tumor uptake. Body mass index had a positive impact on tumor uptake (SUV_{mean} and SUV_{peak}), which was expected since SUVs are corrected for weight. In addition, this result was not expected to impact our conclusions regarding the effect of peptide amount on tumor uptake compared among groups, since body mass index did not significantly differ among groups.

Technical factors such as acquisition parameters (including type of scanner and acquisition time) and postprocessing can also have a major impact on the quantitative indices derived from PET images. Accordingly, harmonization of imaging protocols is highly important in studies with multiple scanner types. This led to the limitation that partial-volume effect (PVE) correction could not be applied, as this functionality is available only on the Vereos PET/CT scanner. PVE corrections generally improve quantitative accuracy, implying that counts are recovered, especially in areas of heterogeneous uptake or in small lesions (diameter, <2 cm). However, since PVE possibly impacted uptake differences among groups, it is unlikely that the observed correlation trends within 1 group were affected. This is of major importance, since one may expect the PVE to play a part, especially in all lesions of group 1 ($\leq 4.11 \text{ cm}^3$). In addition, since tumor volumes were distributed throughout administered peptide amounts in this group, correlation trends were not affected. Still, even without PVE correction, the digital Vereos PET/CT scanner performs better than the 2 Gemini scanners, and a better quantitative performance is known to have a larger impact on smaller lesions (i.e., group 1). This positive effect could have biased the positive correlation that was observed in this group, since a significantly larger percentage of patients in group 1 was imaged using the Vereos PET/CT than in groups 2 and 3.

The results of this study do not have direct implications on current clinical care. There is no need to adjust the current on-site production procedures of ^{68}Ga -PSMA-11; interpatient differences in administered peptide amount do not affect ^{68}Ga -PSMA-11 tumor uptake, because PSMA saturation does not occur in a population of primary PCa patients with small administered peptide amounts (<5.91 μg). Unfortunately, this result is not directly translatable to therapy, since it is unknown whether administrations of larger peptide amounts ($\sim 250 \mu\text{g}$) will result in full occupation of tumor PSMA receptors. Future research is essential to investigate this peptide saturation threshold to determine the potential impact on PSMA radioligand therapy. Still, this study underlined a safe administration of PSMA-11,

regarding receptor saturation, at doses lower than 5.91 μg . This finding supports the European Association of Nuclear Medicine guideline with suggested maximum peptide doses of 6 μg regarding toxicity (23).

CONCLUSION

Overall, the administered peptide amount had no evident effect on ^{68}Ga -PSMA-11 uptake in prostatic tumors in patients with primary PCa, and this finding was also not dependent on lesion volume. Only for patients with small tumor lesion volumes the administered peptide amount showed a significant positive correlation with tumor SUV_{mean} . Still, these findings imply that no receptor saturation occurs in men with primary PCa after administration of peptide levels of approximately 2.5 μg of PSMA-11.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Can the administered peptide amount affect ^{68}Ga -PSMA-11 tumor uptake, and is this potential effect dependent on tumor volume?

PERTINENT FINDINGS: The administered peptide amount did not significantly affect tumor uptake, except for a significant positive low correlation for patients with the smallest index lesions, and lesion volume did not modify the effect of administered peptide amount on tumor uptake. These findings imply that no receptor saturation occurred in this population of primary PCa patients with small administered peptide amounts ($\sim 2.5 \mu\text{g}$).

IMPLICATIONS FOR PATIENT CARE: Since PSMA saturation does not occur after administration of small peptide amounts, there is no need to adjust current on-site production procedures for ^{68}Ga -PSMA-11.

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