ORIGINAL ARTICLE

^{68}Ga-PSMA-11 PET/CT-derived metabolic parameters for determination of whole-body tumor burden and treatment response in prostate cancer

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Abstract

Purpose We aimed at evaluating the role of ^{68}Ga-PSMA-11 PET/CT-derived metabolic parameters for assessment of whole-body tumor burden and its capability to determine therapeutic response in patients with prostate cancer.

Methods A total of 142 patients with biochemical recurrence of prostate cancer underwent PET/CT with [^{68}Ga]Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11). Quantitative assessment of all 641 ^{68}Ga-PSMA-11-positive lesions in the field of view was performed to calculate PSMA-derived parameters, including whole-body PSMA tumor volume (PSMA-TV) and whole-body total lesion PSMA (TL-PSMA), as well as the established SUVmax and SUVmean values. All PET-derived parameters were tested for correlation with serum PSA levels and for association with Gleason scores.

In 23 patients who underwent ^{68}Ga-PSMA-11 PET/CT before and after therapy with either external beam radiation, androgen deprivation, or docetaxel chemotherapy, SUVmax and TL-PSMA were compared to radiographic response assessment of CT images based on RECIST 1.1 criteria and to biochemical response determined by changes of serum PSA levels.

Results PSMA-TV and TL-PSMA demonstrated a significant correlation with serum PSA levels ($P < 0.0001$) and TL-PSMA was significantly different for different Gleason scores. The agreement rate between TL-PSMA derived from PET and biochemical response was 87% (95% confidence interval, 0.66–0.97; Cohen's $\kappa = 0.78$; $P < 0.01$) and, thus, higher than for SUVmax, which was 74% (95% CI, 0.52–0.90; $\kappa = 0.55$; $P < 0.01$). Furthermore, agreement with PSA was higher for TL-PSMA and SUVmax than for CT-based response evaluation. Discordant findings between PET and CT were most likely due to limitations of CT and RECIST in rating small lymph nodes as metastases, as well as bone involvement, which was sometimes not detectable in CT.

Conclusion ^{68}Ga-PSMA-11 PET/CT-derived metabolic tumor parameters showed promising results for evaluation of treatment response. Especially, TL-PSMA demonstrated higher agreement rates with biochemical response compared to SUVmax. Larger, ideally prospective trials are needed to help to reveal the full potential of metabolic parameters derived from PET imaging with ^{68}Ga-PSMA-11.

Keywords ^{68}Ga-PSMA-11 PET/CT · Prostate cancer · Metabolic tumor parameters · Treatment response Whole-body tumor burden

Introduction

Biochemical recurrence in prostate cancer (PC) is a major clinical problem, occurring in up to 30% of patients after radical prostatectomy [1] and in up to 60% of patients after primary external beam radiation therapy [2].

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Initially, PC predominantly metastasizes to lymph nodes and bone; in the later stages, liver and lung can also be affected [3]. Exact detection of recurrence sites is of utmost importance to facilitate therapy planning. For this purpose, an imaging tool with high sensitivity and specificity is needed.

Recently, PET-compatible small-molecule inhibitors, targeting the prostate-specific membrane antigen (PSMA), a surface protein expressed 100- to 1000-fold higher in PC cells than in benign prostate tissue or normal tissue of most other organs, were proposed for PC imaging [4]. PET/CT with [^{68}Ga]Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11) has proven to be an excellent tool for staging and restaging of PC [5, 6], offering superior diagnostic accuracy compared to conventional imaging modalities and choline PET [7]. Assessment of treatment response on PET/CT is primarily based on the appearance or disappearance of PET-positive lesions and on standardized uptake value (SUV) measurements [8]. However, for determination of overall response to therapy, individual lesion SUV measurements might be inadequate and the revised RECIST 1.1 criteria are of limited use in the assessment of bone lesions [9]. Furthermore, it is well known that serum PSA levels do not correlate with the size or number of tumor lesions [10], limiting the applicability of these metrics for response assessment. Therefore, especially for evaluation of therapy response, a parameter reflecting the whole-body tumor burden based on the size, number, and metabolic activity of tumor lesions, which is also easily applicable in clinical practice is urgently needed.

For ^{18}F-FDG-PET/CT, such concepts already exist: For example, it has been demonstrated that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are able to predict poor response, as well as progression-free survival in patients with oesophageal adenocarcinoma who underwent induction chemotherapy [11]. In patients with diffuse large B-cell lymphoma, MTV was measured on ^{18}F-FDG-PET/CT before and after two cycles of chemotherapy, being the only statistically significant predictor of progression-free survival [12].

To the best of our knowledge, the concept of whole-body tumor burden in patients with PC has so far only been assessed in one previous study by Schmuck et al. [13], in which up to a maximum of ten PSMA-positive lesions in the field of view (FOV) were included for determining the whole-body tumor load in a total of 101 patients.

Consequently, the aim of this study is to extend this previous work in a larger number of patients and by including all lesions in the FOV for calculation of metabolic parameters, as well as to compare PET findings with biochemical and RECIST 1.1 evaluations for patients who have been imaged multiple times for assessment of therapeutic response.

Materials and methods

Patients

A total of 142 patients who were referred due to biochemical recurrence of PC between March 2014 and October 2017 were retrospectively included in this study. The patients conformed to the following criteria:

– Histopathologically confirmed PC
– Completed primary therapy (prostatectomy with or without lymph node dissection or radiotherapy, optionally combined with androgen deprivation therapy)
– Biochemical recurrence of PC
– At least one PSMA-positive lesion on the ^{68}Ga-PSMA-ligand PET/CT scan

The diagnosis of biochemically recurrent disease was carried out by the referring urologist and was based on the criteria outlined in the European Association of Urology (EAU) guidelines on PC [14, 15]. These define a biochemical recurrence of PC after radical prostatectomy by two consecutive PSA values of >0.2 ng/mL and rising, and after radiation therapy as rising PSA level > 2 ng/ml above the nadir PSA. The diagnosis of recurring disease was solely based on these criteria.

For each patient, a complete medical history including histology of confirmed PC (primary Gleason score), PSA values, past and present PC therapies, and demographic information was collected. Twenty-three patients underwent ^{68}Ga-PSMA-ligand PET/CT before initiation and after completion of therapy. Patient characteristics are summarized in Tables 1 and 2.

^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11) is an investigational radiopharmaceutical and is not yet US Food and Drug Administration- (FDA) or European Medicines Agency (EMA)-approved. It was therefore used under the conditions outlined in §13(2b) of the Arzneimittelgesetz (AMG; German Medicinal Products Act). Our protocol was approved by the Institutional Review Board of the University Hospital Erlangen, and written informed consent was obtained from all patients.

Radiosynthesis and formulation of ^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11)

The fully automated good manufacturing practice (GMP)-compliant radiosynthesis of Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBED-CC)] (short terms: ^{68}Ga-PSMA-HBED-CC, also known as ^{68}Ga-PSMA-11) was performed as described previously [16], with only slight modifications. ^{68}Ga^{3+} was obtained from the ^{68}Ge/^{68}Ga radionuclide pharmacy-grade generator (1850 MBq, GalliaPharm™, Eckert & Ziegler AG, Berlin, Germany). The final formulation of ^{68}Ga-PSMA-11 was done using isotonic phosphate-buffered

Table 1 Patient characteristics of the entire study population

Parameter	Value
Patient number	142
^{68}Ga-PSMA-11-positive lesions	641
Age	
Mean ± SD	70 ± 8 y
Range	53–89 y
Primary treatment	
Radical prostatectomy	62
Radical prostatectomy + adjuvant radiotherapy	54
Primary radiotherapy	26
Primary Gleason score	
Gleason 6	7
Gleason 7	39
Gleason 8	36
Gleason 9	57
Gleason 10	3
Median	8
Range	6–10
^{68}Ga-PSMA-11-positive lesions	
Total	641
Mean ± SD	4.5 ± 8.2
Range	1–82
Androgen deprivation therapy (%)	
Present	31
Absent	111
PSA (ng/ml)	
Mean ± SD	7.1 ± 11.4
Range	0.1–101.0
Pattern of metastatic spread as defined by PET	
Local	19
Lymph nodes	56
Bone	31
Local + lymph nodes	10
Local + bone	2
Lymph nodes + bone	15
Local + lymph nodes + bone	3
Visceral	1
Visceral + lymph nodes	3
Visceral + bone	1
Visceral + lymph nodes + bone	1

Table 2 Patient characteristics of patients who underwent pre- and post-therapeutic ^{68}Ga-PSMA-11 PET/CT

Parameter	Value
Patient number	23
^{68}Ga-PSMA-11-positive lesions	223
Age	
Mean ± SD	71 ± 8 y
Range	53–90 y
Primary treatment	
Radical prostatectomy	8
Radical prostatectomy + adjuvant radiotherapy	5
Primary radiotherapy	8
Chemotherapy	2
Primary Gleason score	
Median	8
Range	6–10
Treatment after first ^{68}Ga-PSMA-11 PET/CT	
Radiation therapy	13
Androgen deprivation therapy	9
Chemotherapy	1
Androgen deprivation therapy (%)	
Present	10
Absent	13
PSA (ng/ml)	
Mean ± SD	8.9 ± 14.4
Range	0.5–90.0
Pattern of metastatic spread as defined by PET	
Local	1
Lymph nodes	5
Bone	6
Local + lymph nodes	1
Lymph nodes + bone	7
Local + lymph nodes + bone	2
Visceral + bone	1

saline (PBS) and sterile filtration of 14.5 mL. The radiochemical yield of ^{68}Ga-PSMA-11 was 54 ± 5% (referred to the eluted [68]Ga^{3+}) and the radiochemical purity was >96% as determined by radio-HPLC [Chromolith Performance RP-18e, 100 × 4.6 mm, 5% acetonitrile (0.1% TFA; 0–0.5 min), 5–80% acetonitrile (0.1% TFA; 0.5–10 min), 2 mL/min, 280 nm]. The solution of ^{68}Ga-PSMA-11 was applied to the patient via an intravenous bolus injection (mean of 134 ± 36 MBq).

Imaging procedure

^{68}Ga-PSMA-11 PET/CT imaging was performed using a dedicated PET/CT system (Biograph mCT scanner, Siemens Medical Solutions).

A fully diagnostic, contrast-enhanced CT scan (120 kV, 170 mAs, 16 × 1.2-mm slice collimation, 0.5-s rotation time, pitch 1, reconstructed with filtered backprojection using B30f and B70f kernels, slice thickness 1.5 mm, and increment 1 mm) after injection of Imeron 350 at 1.5 ml/kg body weight was performed 1 h post-injection (p.i.) of ^{68}Ga-PSMA-11 in a mean radioactivity of 134 ± 36 MBq. Immediately after CT scanning, a whole-body PET scan (skull base to mid-thighs) was acquired (3 min per bed, axial FOV of 21.8 cm per bed). The PET data were corrected for random and scattered

coincidences, as well as for decay during scanning. PET data was corrected for attenuation by using the CT and reconstructed with an ordered subset expectation maximization (OSEM) algorithm with 2 iterations/12 subsets and point-spread-function modeling (Siemens TrueX). All corrections and reconstructions were carried out using the manufacturer's software available on the PET/CT system.

Image analysis

All PET/CT datasets were analyzed with commercially available software (Syngo.via, Siemens Molecular Imaging, Hoffman Estates, IL, USA), allowing review of PET, CT, and fused imaging data. Visual evaluation was performed by two experienced nuclear medicine physicians and one radiologist. Diagnostic decisions were made by consensus.

PET image analysis

Excluding structures with known non-malignant uptake of PSMA (e.g. salivary glands and celiac ganglia), all remaining lesions with visually higher uptake than the respective normal region (gluteal muscle/lumbar vertebral body) were rated as PSMA-positive, suggesting local recurrence or metastases. For all suspected pathological lesions ($n = 641$), the mean and maximum SUV (SUVmean, SUVmax) and the MTV of each lesion was determined in VOIs with isocontours set at 45% of the maximum uptake within the respective focus.

From these parameters, each lesion's PSMA uptake was calculated by multiplying the respective MTV and mean SUV (Fig. 1). Following the suggestions of Schmuck et al. [13], this parameter is called total lesion PSMA or TL-PSMA and the MTV is called PSMA total volume or PSMA-TV. Furthermore, per-patient and per-lesion average values of the four mentioned parameters were calculated.

Summation of the MTV over all lesions of a patient resulted in the whole-body PSMA-TV (wbPSMA-TV) summation of the PSMA uptake over all patient lesions in the whole-body TL-PSMA (wbTL-PSMA).

Response to treatment analysis

In 23 patients who underwent ^{68}Ga-PSMA-11 PET/CT at baseline and for follow-up after therapy, radiographic response to treatment was assessed independently in PET and CT and compared to biochemical response (BR) based on PSA serum levels. Of the 23 patients, 13 patients underwent external beam radiation therapy, 9 patients androgen deprivation therapy, and 1 patient docetaxel chemotherapy. In detail, the response criteria were as follows:

Biochemical Response

- BR was assessed by measuring serum PSA level. To be consistent with other studies [17–19], BR criteria for complete and partial response (PR/CR) and for stable and
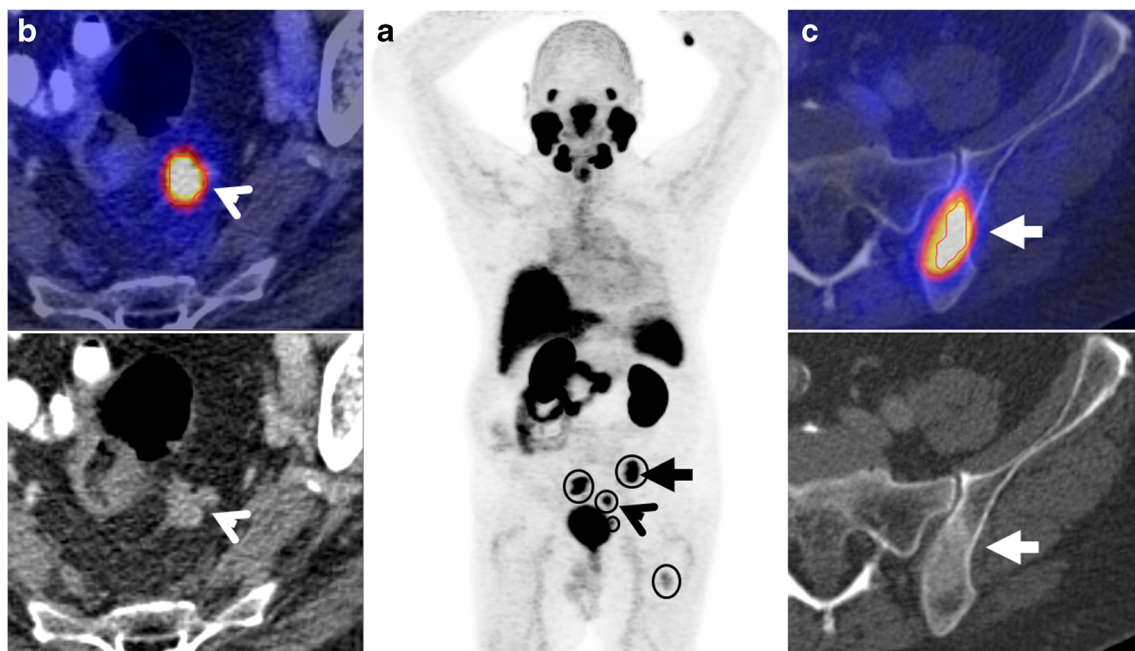

Fig. 1 Assessment of whole-body tumor burden by ^{68}Ga-PSMA-11 PET/CT in a 78-year-old patient (patient # 15 in Table 6), Gleason 8 tumor, serum PSA at examination 23 ng/ml with metastasized prostate cancer. The maximum intensity projection (**a**) shows several ^{68}Ga-PSMA-11-positive metastases (indicated by circles). The left and right panels respectively demonstrate the segmentation of a lymph node metastasis (**b**, arrowhead) and a bone metastasis (**c**, arrow) to determine tumor volume and intensity of tracer uptake for calculation of PSMA-TV and TL-PSMA

progressive disease (SD/PD) were adapted accordingly and are given in Table 3.

Radiographic response in PET (RR-PET)

Per patient, five organ systems comprising lymph nodes, bone, liver, prostate/prostate bed, and other visceral metastatic sites were used for analysis. For each organ system, the two lesions with the highest SUVmax and with the highest TL-PSMA in the first PET examination were independently determined and selected as target lesions. However, only up to a maximum of five target lesions were selected for further evaluation in order to conform with the RECIST 1.1 criteria in this regard. SUVmax and TL-PSMA were determined as previously described and summed up for all target lesions.

According to slightly modified PET Response Criteria in Solid Tumors (PERCIST) 1.0 [20], post-treatment changes were interpreted as provided in Table 3.

In the following, the radiographic response as determined for SUVmax and TL-PSMA is referred to as RR-PET (SUVmax) and RR-PET (TL-PSMA), respectively.

Radiographic response in X-ray CT (RR-CT)

Radiographic response to treatment was assessed according to RECIST 1.1 criteria [21]: The exact same lesions as in the PET response evaluation were selected as target lesions in CT. Since target lesions for RR-PET (SUVmax) and RR-PET (TL-PSMA) evaluation could be potentially different from each other, two potentially different sets of CT target lesions for each patient exist, one derived from PET SUVmax target lesions and another derived from PET TL-PSMA target lesions. Both sets of CT target lesions for each patient were independently processed and results are provided separately. Within each set of target lesions, all diameters were summed (longest for non-nodal lesions, short axis for nodal lesions). Bone metastases were assessed in terms of unequivocal progression. Post-treatment changes were interpreted as given in Table 3:

In the following, the radiographic response as determined for CT, based on target lesions defined by SUVmax and TL-PSMA is referred to as RR-CT (SUVmax) and RR-CT (TL-PSMA), respectively.

Statistical analysis

Descriptive statistics were computed for continuous and categorial variables, including mean, standard deviations (SD), and range for continuous variables and absolute and relative frequencies for categorial variables.

Correlation between PET-derived parameters and PSA levels were analyzed by using Spearman's rank correlation.

A one-way analysis of variance (ANOVA) was used to evaluate whether SUVmax, SUVmean, wbPSMA-TV, and wbTL-PSMA were different for the patient groups with a Gleason score ≤ 7, Gleason $= 8$, and Gleason ≥ 9.

For the response-to-treatment analysis, classifications based on SUVmax, TL-PSMA, serum PSA-levels, and RECIST 1.1 criteria are listed individually.

Furthermore, the degree of agreement between radiographic and BR assessment was determined by calculation of percent agreement and Cohen's κ [22], including 95 % confidence intervals (95% CIs) for the agreement and level of significance for κ. In this context, interpretation of κ was based on a classification provided by Landis and Koch [23]: 0.0, poor; 0.0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect agreement.

For all analyses, a P value < 0.05 was considered statistically significant. Statistical analyses were performed using Matlab version R2012b (The Math Works Inc., Natick, MA, USA).

Results

Descriptive statistics

In 142 patients, a total of 641 lesions were detected. A total of 361 lymph node metastases were found in 88 (62%) patients,

Table 3 Criteria for therapeutic response assessment

	Complete response	Partial response	Stable disease	Progressive disease
BR	PSA ≤ 50%	50% < PSA ≤ 75%	75% < PSA ≤ 125%	PSA > 125%
PET	∅ malignant PSMA uptake	SUVmax ≤ 70% or TL-PSMA ≤ 70%	70% < SUVmax < 130% or 70% < TL-PSMA < 130%	New PSMA-pos. lesion or SUVmax, TL-PSMA ≥ 130%
CT	Disappearance of lesions	Diam. ≤ 70%	70% < Diam. < 120% and ∅ new target lesion	New target lesion or diam ≥ 120%, at least +5 mm

All criteria are relative to their respective baseline values. In PET and CT, the criteria are summed values over up to five target lesions.

BR biochemical response, *PSA* serum value of prostate-specific antigen, *TL-PSMA* total lesion prostate-specific membrane antigen uptake, *Diam.* lesion diameter as measured in CT

239 bone metastases in 53 (37%) patients, 34 local recurrences in 34 (24%) patients, and 7 other metastases in 5 (4%) patients. On average, 4.5 ± 8.2 lesions (range 1–82) were found per patient.

Only one ^{68}Ga-PSMA-11-positive lesion in the FOV was found for 53 (37%) patients, while 89 (63%) had more than 1 lesion.

The number of patients at a respective Gleason score was: 7 patients with Gleason score = 6, 39 patients with Gleason score = 7, 36 patients with Gleason score = 8, 57 patients with Gleason score = 9, and 3 patients with Gleason score = 10.

Mean, SD, and range of the four PET parameters SUVmean, SUVmax, PSMA-TV, and TL-PSMA are summarized in Table 4 on per-patient and per-lesions bases.

Correlation of serum PSA levels with PET parameters

SUVmean, SUVmax, wbPSMA-TV, and wb TL-PSMA correlated with serum PSA levels in a significant way.

For those patients with more than one lesion ($n = 89$), only SUVmax, wbPSMA-TV, and wbTL-PSMA correlated with serum PSA levels at a statistically significant level, while in patients with only one lesion ($n = 53$), all four parameters correlated significantly with PSA.

When analyzing for mean value differences between the Gleason groups, only the parameter wbTL-PSMA was significantly different (one-way ANOVA $P < 0.05$; Fig. 2).

An overview of the correlation between the four PET parameters and the serum PSA levels is provided in Table 5, for all patients, as well as for the respective subgroups, including correlation parameters and significance levels.

Additionally, from the plot of wbPSMA-TV versus PSA serum level (Fig. 3), the correlation can be seen.

Table 4 Volumetric ^{68}Ga-PSMA-11 PET/CT parameters and intensity of tracer uptake on a per-patient and a per-lesion basis

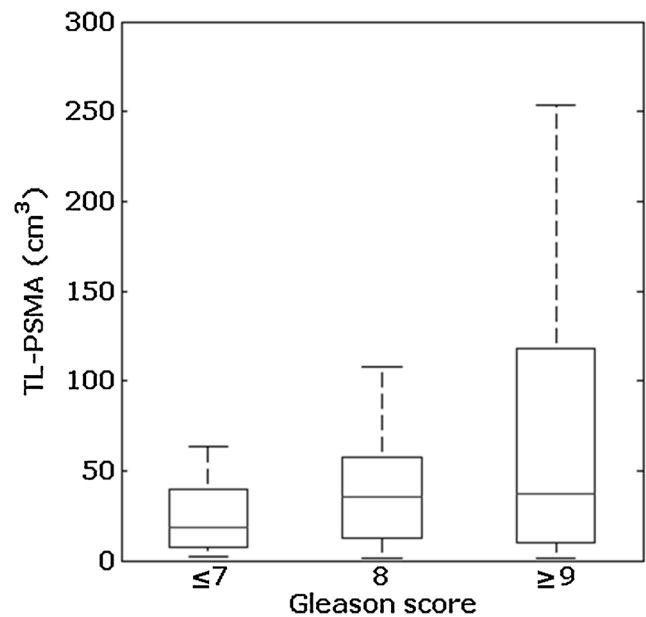|	Per-lesion basis	Per-patient basis
Uptake intensity of ^{68}Ga-PSMA-11-positive lesions		
SUV max		
Mean ± SD	16.4 ± 19.9	26.2 ± 30.2
Range	1.2–190.0	1.2–190.0
SUV mean		
Mean ± SD	10.9 ± 13.2	10.5 ± 10.5
Range	0.8–122.2	0.8–58.2
PSMA-TV (cm³)		
Mean ± SD	1.7 ± 2.1	7.4 ± 10.4
Range	0.2–22.4	0.2–68.5
TL-PSMA (cm³)		
Mean ± SD	17.1 ± 39.8	73.8 ± 144.1
Range	0.5–620.9	1.6–1031.1

Fig. 2 TL-PSMA shows a significant correlation with primary Gleason scores and is also significantly different between different Gleason scores

Evaluation of response to therapy by using biochemical, PET, and CT criteria

A total of 23 patients with 223 ^{68}Ga-PSMA-11-positive lesions which received baseline and follow-up ^{68}Ga-PSMA-11-PET/CT were included in the therapeutic response evaluation, consisting of 13 patients who underwent radiation therapy, 9 patients who underwent androgen deprivation therapy, and 1 patient who underwent chemotherapy (see Fig. 4 for ^{68}Ga-PSMA-11-PET/CT imaging in a patient who underwent baseline and follow-up PET/CT after radiation therapy of a PSMA-positive lymph node metastasis).

Based on the BR, 2 patients were diagnosed with CR, 9 with PR, 1 with SD, and 11 with PD. With assessment of response based on SUVmax from PET, 2 patients were diagnosed with CR, 6 with PR, 0 with SD, and 15 with PD. Based on the measurement of TL-PSMA, 2 patients were diagnosed with CR, 7 with PR, 0 with SD, and 14 with PD. For the response assessment based on CT target lesions as defined by the SUVmax criterion, 1 patient was diagnosed with CR, 4 with PR, 8 with SD, and 10 with PD. For CT target lesions defined by the TL-PSMA criterion, one patient was diagnosed with CR, seven with PR, six with SD, and nine with PD. A detailed overview of each patient's response evaluation is provided in Table 6.

The agreement between BR and RR-PET (SUVmax) was 74% and between BR and RR-PET (TL-PSMA) 87%. The agreement of BR and RR-CT (SUVmax) was 39% and for BR and RR-CT (TL-PSMA) 56%. The agreement between RR-PET (SUVmax) and RR-CT (SUVmax) was 56%. The agreement of RR-PET (TL-PSMA) and RR-

Table 5 Overview of correlation of ^{68}Ga-PSMA-11 PET-derived parameters with serum PSA level for all patients and subgroups

PET parameter	Correlation with serum PSA level given as Spearman's rank correlation coefficient					
	All patients ($n = 142$)	Patients w. more than one lesion ($n = 53$)	Patients w. one lesion only ($n = 89$)	Patients w. Gleason ≤ 7 ($n = 46$)	Patients w. Gleason $= 8$ ($n = 36$)	Patients w. Gleason ≥ 9 ($n = 60$)
SUVmax	0.38 (**)	0.23 (*)	0.40 (**)	0.34 (*)	0.45 (**)	0.38 (**)
SUVmean	0.26 (**)	0.16 (n.s.)	0.40 (**)	0.16 (n.s.)	0.36 (*)	0.24 (n.s.)
wbPSMA-TV	0.48 (**)	0.43 (**)	0.14 (n.s.)	0.31 (*)	0.40 (*)	0.61 (**)
wbTL-PSMA	0.54 (**)	0.41 (**)	0.41 (**)	0.41 (**)	0.44 (**)	0.64 (**)

The level of significance is indicated by one asterisk (*) for $P < 0.05$, two asterisks (**) for $P < 0.01$, and (n.s.) for non-significant values

CT (TL-PSMA) was 61%. An overview of the agreement is provided in Table 7, along with a 95% CI for the agreement, Cohen's Kappa values, and level of significance for Cohen's Kappa.

Discussion

In the current work, we were able to significantly extend the previous study of Schmuck et al. [13] by increasing the population to 142 patients and the analyzed lesion number to 641 lesions. Additionally, we analyzed baseline and follow-up PET/CT data of 23 patients under therapy and compared response evaluation based on PSA serum levels, PET-derived SUVmax and TL-PSMA, and CT-derived PERCIST.
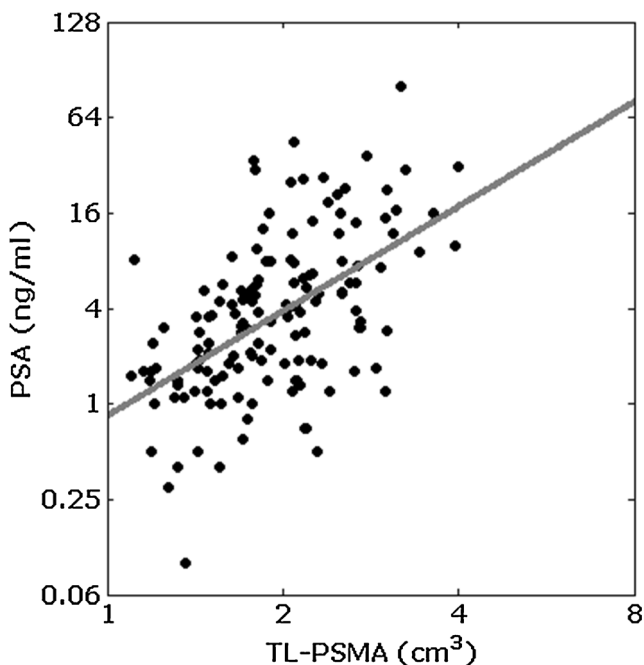

Fig. 3 TL-PSMA demonstrates a significant correlation with PSA levels ($r = 0.53$, $P < 0.0001$)

Correlation of PSA and PET-derived metabolic parameters

We could demonstrate that SUVmean, SUVmax, whole-body PSMA-TV, and whole-body TL-PSMA correlated significantly with serum PSA levels in our patient population.

In the comparable study of Schmuck et al. [13], the authors found a significant correlation of whole-body PSMA-TV and whole-body TL-PSMA with serum PSA levels, which is analogous to our results. Nevertheless, some differences between their results and ours are present. For example, their results suggested no correlation of SUVmax and SUVmean values with serum PSA levels. The differences might be explainable due to the higher patient number (101 vs. 142) and higher number of ^{68}Ga-PSMA-11-positive lesions (304 vs. 641) which were evaluated in our study.

Furthermore, deviating results for correlation of SUVmax and SUVmean with PSA could be explained by differences of the number of patient lesions of the study populations. When analyzing the sub-groups of patients which have more than one or only one ^{68}Ga-PSMA-11-positive lesion, we found that the correlation of SUVmax and SUVmean with PSA was higher for the latter group. Most likely, in patients with only one lesion, SUVmean and SUVmax are surrogate parameters which express the entire tumor load of a patient as sufficient as PSA, PSMA-TV, and TL-PSMA. However, since we do not have detailed knowledge on the Schmuck et al. patient population in this regard, this is speculative.

Interestingly, we found that TL-PSMA was the only parameter which was significantly different for primary Gleason score, while other PET-derived parameters like SUVmax, SUVmean, and PSMA-TV were not. An explanation for this might be that in contrast to PSMA-TV, which only takes into account the MTV, TL-PSMA also considers the degree of PSMA-expression of tumor cells which is regularly elevated at higher Gleason scores [24, 25].
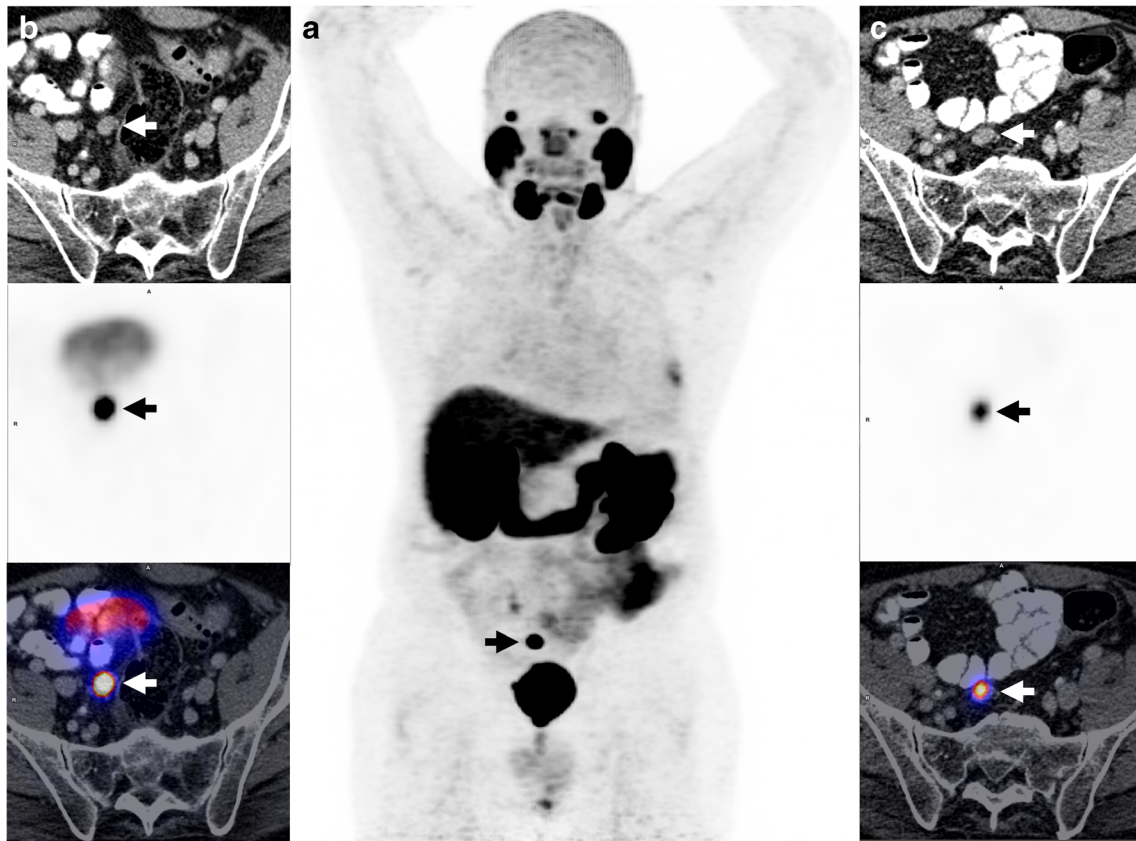
Fig. 4 ^{68}Ga-PSMA-11 PET/CT-derived metabolic parameters for assessment of therapeutic response in a 71-year-old patient (patient # 10 in Table 6), Gleason 7 tumor, and serum PSA at first examination of 1.7 ng/ml. Maximum intensity projection (**a**). Baseline (**b**) and follow-up PET/CT after radiation therapy (**c**) demonstrate a ^{68}Ga-PSMA-11- positive metastasis in the pelvis (arrow). Serum PSA level at second examination decreased by 30% (biochemical PR), SUVmax decreased by 38% (RR-PET PR), TL-PSMA decreased by 48% (RR-PET PR), while radiographic response assessment based on CT indicated stable disease (SD)

Monitoring of response to treatment

Currently, assessment of therapeutic response in PC is based on changes of serum PSA levels, on the evaluation of X-ray CT imaging, using the RECIST 1.1 criteria, and other clinical outcome parameters [26]. Little is known about the role of hybrid imaging and especially the potential of PET/CT in this regard. A few reports on the use of ^{18}F-choline and ^{11}C-choline PET/CT are available [27–29]. Also, information on the role of PSMA PET/ CT in monitoring response to treatment and on enhanced metabolic PET parameters such as TL-PSMA and PSMA-TV is scarce and only a few reports are available. In the ^{68}Ga-PSMA-ligand PET/CT study of Seitz et al. [30], a comparison between response monitoring based on PET and on RECIST 1.1 CT evaluation was performed. In 23 patients undergoing docetaxel chemotherapy, they found that response assessment with PET showed a higher concordance to changes of PSA serum levels, compared to the RECIST 1.1 evaluation. These differences were not statistically significant, which the authors attribute to the too limited number of patients in the study.

In the study of Schmuck et al. [13], response-to-treatment assessment with PET was compared to changes in PSA level. Specifically, the correlation between changes in PSA level and PET-derived parameters SUVmax, SUVmean, PSMA-TV, and TL-PSMA were calculated. The authors found that changes in PSMA-TV and TL-PSMA correlated significantly with changes of PSA, while no such correlation was found for SUVmax and SUVmean. The authors thus conclude that PSMA-TV and TL-PSMA might facilitate therapy monitoring.

Congruently, our results also suggest a potential superiority of parameters derived from ^{68}Ga-PSMA-11 PET over X-ray CT in assessing response of PCA to treatment. Agreement between SUVmax/TL-PSMA and BR evaluation was substantially higher compared to the agreement between CT assessment based on RECIST 1.1 and BR, although this difference did not reach statistical significance. Notably, similar to the results of Schmuck et al., the agreement to BR assessment was higher for TL-PSMA than for SUVmax values, although the difference was not statistically significant as well.

An explanation for the potential superiority of TL-PSMA could be that while SUVmax represents the highest metabolic

Table 6 Individual patient results of the response assessment based on biochemical response (BR), radiographic response (RR) in PET for the parameters SUVmax and TL-PSMA, as well as for the radiographic response in CT using RECIST 1.1 criteria

Patient	BR	RR-PET (SUVmax)	RR-CT (SUVmax)	RR-PET (TL-PSMA)	RR-CT (TL-PSMA)
1	PR	PR	SD	PR	PR
2	PD	PD	PD	PD	PD
3	PR	PR	SD	PR	SD
4	PR	PD	PD	PR	PR
5	PR	PD	SD	PD	SD
6	PD	PD	SD	PD	SD
7	PR	PR	SD	PR	SD
8	PR	PD	SD	PD	SD
9	PD	PR	PR	PD	PR
10	PR	PR	SD	PR	SD
11	PD	PD	PD	PD	PD
12	CR	CR	CR	CR	CR
13	PD	PD	PD	PD	PD
14	PD	PD	PD	PD	PD
15	PD	PD	PD	PD	PD
16	PD	PD	SD	PD	PD
17	PD	PD	PR	PD	PR
18	PR	PR	PR	PR	PR
19	CR	CR	PR	CR	PR
20	PD	PD	PD	PD	PD
21	PR	PD	PD	PR	PR
22	PD	PD	PD	PD	PD
23	SD	PD	PD	PD	PD
	2/9/1/11 CR/PR/SD/PD	2/6/0/15 CR/PR/SD/PD	1/4/8/10 CR/PR/SD/PD	2/7/0/14 CR/PR/SD/PD	1/7/6/9 CR/PR/SD/PD

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

activity of a single voxel within the tumor, TL-PSMA also takes into account the MTV of metastatic lesions.

Limitations

Our study suffers from several limitations. First of all, due to the low number of only 23 patients who underwent baseline and follow-up PET/CT for evaluation of therapeutic response, the results have to be interpreted with caution. Possible biases stemming from patient referrals and treatments cannot be excluded due to the retrospective nature of this analysis. Furthermore, this analysis was conducted as a single-center study and histological confirmation as a gold standard of each PSMA-positive lesion would have been preferable, but was not feasible.

Table 7 Comparison of agreement between ^{68}Ga-PSMA-11 PET-derived radiographic response (RR-PET) using TL-PSMA and SUVmax with response assessment on CT (RR-CT) and biochemical response (BR) based on serum PSA levels

		Agreement (%)	95% Confidence interval of agreement	Cohen's Kappa	*P* value
TL-PSMA (*n* = 23)					
BR	RR-PET (TL-PSMA)	87	0.66–0.97	0.78	<0.01
BR	RR-CT (TL-PSMA)	56	0.35–0.77	0.36	<0.05
RR-PET (TL-PSMA)	RR-CT (TL-PSMA)	61	0.39–0.80	0.42	<0.05
SUVmax (*n* = 23)					
BR	RR-PET (SUVmax)	74	0.52–0.90	0.55	<0.01
BR	RR-CT (SUVmax)	39	0.20–0.62	0.14	0.4
RR-PET (SUVmax)	RR-CT (SUVmax)	56	0.31–0.73	0.35	0.05

While PERCIST 1.0 criteria are already established for evaluation of therapeutic response in FDG-PET studies [31], there are as yet no established standardized response criteria for PSMA-PET. As a surrogate, we adapted PERCIST 1.0 criteria for assessment of treatment response, which could potentially overcome several limitations of solely morphological-based criteria. For example, lesions, e.g. bone metastases without soft tissue mass > 10 mm, which are rated unmeasurable by RECIST 1.1 criteria [21] could now be included in the evaluation. Consequently, MTV could be addressed directly, instead of lesion diameter sums [32]. Thus, e.g. TL-PSMA, combining metabolic tumor activity and MTV, might be an ideal parameter for therapeutic response evaluation. Nevertheless, although other groups used the same modified PERCIST criteria for PSMA-PET [33] as we did, the response thresholds have to be validated in larger studies.

Lastly, radiographic response assessment was compared to BR as measured by PSA serum levels, which is also recommended for assessment of many therapies in advanced PC by the current guidelines of the EAU [34]. However, Ceci et al. [17] and the EAU recommendations for therapy monitoring in patients with advanced castration-resistant prostate cancer (CRPC) pointed out that PSA alone might not be sufficiently reliable for assessment of treatment response in all cases.

To determine the validity of radiographic response assessment, long-term follow-up and survival in treated patients should be evaluated in larger prospective multicenter trials.

Conclusion

SUVmean and SUVmax, as well as advanced PET-derived parameters which express the total MTV, such as whole-body PSMA-TV and TL-PSMA, demonstrated a significant correlation with serum PSA levels. TL-PSMA was the only PET-derived parameter which was significantly different between patient groups with different Gleason scores. Additionally, response-to-therapy assessment using TL-PSMA showed the highest agreement to monitoring based on PSA levels, superior to SUVmax-based evaluation and response assessment based on CT data and RECIST 1.1 criteria.

Altogether, this suggests a possible role of ^{68}Ga-PSMA-11 PET/CT for therapeutic response evaluation in patients with PC.

Compliance with ethical standards

Ethical approval 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 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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