
Initial Experience with Volumetric ^{68}Ga -PSMA I&T PET/CT for Assessment of Whole-Body Tumor Burden as a Quantitative Imaging Biomarker in Patients with Prostate Cancer

Sebastian Schmuck¹, Christoph A. von Klot², Christoph Henkenberens³, Jan M. Sohns¹, Hans Christiansen³, Hans-Jürgen Wester⁴, Tobias L. Ross¹, Frank M. Bengel¹, and Thorsten Derlin¹

¹Department of Nuclear Medicine, Hannover Medical School, Hannover, Germany; ²Department of Urology and Urologic Oncology, Hannover Medical School, Hannover, Germany; ³Department of Radiation Oncology, Hannover Medical School, Hannover, Germany; and ⁴Pharmaceutical Radiochemistry, Technische Universität München, Garching, Germany

A quantitative imaging biomarker is desirable to provide a comprehensive measure of whole-body tumor burden in patients with metastatic prostate cancer, and to standardize the evaluation of treatment-related changes. Therefore, we evaluated whether prostate-specific membrane antigen (PSMA) ligand PET/CT may be applied to provide PSMA-derived volumetric parameters for quantification of whole-body tumor burden. **Methods:** One hundred one patients who underwent ^{68}Ga -PSMA I&T PET/CT because of increasing prostate-specific antigen (PSA) levels after radical prostatectomy were included in this retrospective analysis. Tracer uptake was quantified using SUVs. Volumetric parameters, that is, PSMA-derived tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA), were calculated for each patient using a 3-dimensional segmentation and computerized volumetry technique and compared with serum PSA levels. In a group of 10 patients, volumetric parameters were applied for treatment monitoring. **Results:** Volumetric parameters, that is, whole-body PSMA-TV and whole-body TL-PSMA, demonstrated a statistically significant correlation with PSA levels ($P < 0.0001$) as a surrogate marker of tumor burden, whereas SUV_{max} ($P = 0.22$) or SUV_{mean} ($P = 0.45$) did not. Treatment response and treatment failure were paralleled by concordant changes in both whole-body PSMA-TV and whole-body TL-PSMA ($P = 0.02$), whereas neither the change in SUV_{max} ($P = 1.0$) nor the change in SUV_{mean} ($P = 1.0$) concordantly paralleled changes in PSA levels. **Conclusion:** PSMA-derived volumetric parameters provide a quantitative imaging biomarker for whole-body tumor burden, capable of standardizing quantitative changes in PET imaging of patients with metastatic prostate cancer and of facilitating therapy monitoring.

Key Words: PET/CT; tumor volume; MTV; TLG; PSMA

J Nucl Med 2017; 58:1962–1968

DOI: 10.2967/jnumed.117.193581

Prostate-specific membrane antigen (PSMA) has recently gained interest as a molecular target for both clinical imaging and radionuclide therapy of prostate cancer (1–6). PET/CT imaging using ^{68}Ga -PSMA ligands is a highly sensitive method for detection of primary tumors as well as locally recurrent or metastatic lesions after primary prostate cancer treatment (1,4). Accordingly, several PSMA ligands are in routine clinical use (2,5–7). ^{68}Ga -PSMA imaging and therapy (I&T) has recently been demonstrated to localize primary prostate cancer and to provide high detection rates in recurrent prostate cancer (8–10). PSMA I&T can be labeled with either ^{68}Ga or ^{177}Lu for theranostic purposes (6).

PSMA ligand PET images may be semiquantitatively analyzed using SUVs (1). However, treatment-related changes in individual lesion SUV may be inadequate to determine the overall response. There is a need for precise assessment of overall tumor burden, especially in the context of monitoring therapeutic efficacy. The secretion of prostate-specific antigen (PSA) by cancer cells is highly variable and does not correlate with size or grade of prostate tumor lesions (11,12), such that serum PSA is a suboptimal biomarker for assessment of changes in tumor burden. In morphologic imaging, the RECIST allow for assessment of treatment, based on selection of representative individual tumor lesions (13). PET allows sensitive and direct assessment of whole-body tumor burden (14). Therefore, volumetric parameters derived from ^{18}F -FDG PET/CT such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have recently gained prominence for prognostic studies and for treatment monitoring in a variety of cancers, because they provide a direct estimation of whole-body tumor load (14–17). However, ^{18}F -FDG PET/CT has limited value for assessment of prostate cancer. The preferred method for detecting skeletal metastases from prostate cancer is whole-body bone scintigraphy (18,19). However, this method is not specific to tumor cells, does not evaluate extraosseous disease, and does not readily provide volumetric parameters. In addition, the flare phenomenon may be misinterpreted as progression of disease. For all these reasons, a tumor-specific imaging biomarker of whole-body tumor burden would represent a major advance. To our knowledge, the concept of whole-body MTV or TLG assessment has not yet been applied in prostate cancer using PSMA ligands.

Received Mar. 20, 2017; revision accepted May 10, 2017.

For correspondence or reprints contact: Thorsten Derlin, Department of Nuclear Medicine, Hannover Medical School, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany.

E-mail: Derlin.Thorsten@mh-hannover.de

Published online May 18, 2017.

COPYRIGHT © 2017 by the Society of Nuclear Medicine and Molecular Imaging.

Therefore, the aim of this study was to evaluate PSMA ligand PET/CT to assess volumetric parameters as a measure of whole-body tumor burden, in comparison with other image-based parameters and PSA levels as a surrogate marker of tumor load.

MATERIALS AND METHODS

Study Population

The study population of this retrospective study consisted of 101 men (69.1 ± 6.8 y; age range, 49.9–82.6 y) who were referred for ^{68}Ga -PSMA I&T PET/CT for detection of biochemical recurrence or PSA persistence after radical prostatectomy for prostate cancer between November 2014 and March 2016. Patients were selected according to the following inclusion and exclusion criteria. Inclusion criteria were detectable PSA level after radical prostatectomy for primary prostate cancer, detectable lesions on the ^{68}Ga -PSMA I&T PET/CT scan, and available clinical history including initial Gleason score and PSA levels at the time of PET/CT. Exclusion criteria included external-beam radiation therapy or (combined) brachytherapy for primary treatment, local therapy without complete resection of prostate (transurethral resection of the prostate, cryosurgical ablation of the prostate, high-intensity focused ultrasound, irreversible electroporation), and more than 10 PSMA-positive lesions on the ^{68}Ga -PSMA I&T PET/CT scan; the analysis was restricted to patients with 10 or fewer lesions, because nonautomated measurement of tumor volumes (TVs) is time- and labor-intensive.

Details on patient characteristics are summarized in Table 1. All studies were performed during the clinical diagnostic workup of patients. ^{68}Ga -PSMA I&T was administered in compliance with the Declaration of Helsinki, §37, and the German Medicinal Products Act, AMG §13.2b. The institutional review board approved this retrospective study.

Preparation of PSMA-Targeting Ligand

^{68}Ga -PSMA I&T (5,6) was synthesized by a fully automated, good manufacturing practice-compliant procedure (20) using a good

radiopharmaceutical practice module (SCINTOMICS GmbH) connected to a $^{68}\text{Ge}/^{68}\text{Ga}$ generator (1.11-GBq Obninsk Generator; Eckert & Ziegler EUROTOPE GmbH) and equipped with a disposable single-use cassette kit (ABX). A standardized labeling sequence with 22.5 μg (15 nmol) of unlabeled PSMA I&T (SCINTOMICS GmbH) was used. For quality control, ^{68}Ga -PSMA I&T was analyzed by analytic high-performance liquid chromatography according to the monographs 2462 (gallium chloride) and 2482 (gallium edotreotide) of the European Pharmacopoeia. Radioanalytic high-performance liquid chromatography was performed on a ProStar high-pressure gradient system (Varian) equipped with an ultraviolet-visible detector (ProStar 335; Varian) and a radiodetector (Berthold LB 3800-20 with LB 6657 probe) using an RP-18 column (Gemini C18 5 μ 110A, 250 x; Phenomenex). The eluent had a linear gradient from 100% solvent A (phosphate buffer/acetonitrile, 85:15) to 100% solvent B (phosphate buffer/acetonitrile, 65:35) over 25 min at a flow of 0.6 mL/min.

PET/CT Acquisition and Image Reconstruction

All studies were acquired using a dedicated PET/CT system (Biograph mCT 128 Flow; Siemens), equipped with an extended field-of-view PET component, a 128-slice spiral CT component, and a magnetically driven table optimized for continuous scanning. Patients received an intravenous injection of 96 ± 28 MBq of the ^{68}Ga -PSMA ligand. Imaging started with a low-dose nonenhanced helical CT (120 kV, mA modulated, pitch of 1.2, reconstructed axial slice thickness of 5.0 mm) for attenuation correction. Whole-body PET images were subsequently acquired using continuous bed motion at a speed of 0.9 mm/s for chest and abdomen and 2.1 mm/s for legs at 1 h after injection after voiding of the bladder. All studies were reconstructed using Ultra HD, an iterative algorithm combined with time-of-flight and point-spread function information (Siemens Healthcare; 2 iterations, 21 subsets; matrix, 200; zoom, 1.0; gaussian filter, 5.0). No contrast material was administered.

Image Analysis and Calculation of Volumetric Parameters

PET/CT images were analyzed using a dedicated workstation equipped with a commercial software package (syngo.via; V10B; Siemens Healthcare), allowing simultaneous and fused review of PET and CT data. All lesions suggestive for recurrent prostate cancer were noted, and their localization (e.g., local recurrence, lymph node metastases, bone metastases) was recorded (1). For PET images, focal uptake of ^{68}Ga -PSMA I&T higher than background was judged as tissue suspected of malignancy. The number of detected metastases per patient was recorded. To calculate volumetric parameters, an isocontour volume of interest including all voxels above 45% of the maximum was created (Fig. 1) using a 3-dimensional segmentation and computerized volumetric technique, as performed recently in similar studies (9,21). This measurement yielded a PSMA-derived TV (PSMA-TV), similar to the MTV investigated in previous studies (14–17). Next, PSMA-TV was multiplied by SUV_{mean} of the lesion, yielding the total lesion PSMA (TL-PSMA), comparable to the TLG as previously reported (14–17). In addition, SUV_{mean} and SUV_{max} were measured within all volumes of interest. The SUV_{max} threshold of 45% was determined experimentally in 5 representative patient scans by varying the cutoff at 40%, 45%, and 50% to obtain agreement with the contour of the lesions on CT, compensating for activity spill-over. No significant differences were observed concerning PSMA-TV ($P = 0.91$), TL-PSMA ($P = 0.64$), SUV_{max} ($P = 0.51$), and SUV_{mean} ($P = 0.96$) between these 5 scans and the total study population.

The feasibility of volumetric therapy response assessment was investigated in 10 patients who underwent both a baseline and a

TABLE 1
Characteristics of Study Population ($n = 101$)

Parameter	Value
Subjects	101 (100)
Age (y)	
Mean \pm SD	69.1 \pm 6.8
Range	49.9–82.6
Primary Treatment	
Primary radical prostatectomy	101 (100)
Primary Gleason score	
Median	7
Range	6–10
PSA (ng/mL)	
Mean \pm SD	4.1 \pm 10.1
Range	0.13–94.7
ADT (%)	
Present	15 (15)
Absent	86 (85)

Data in parentheses are percentages.

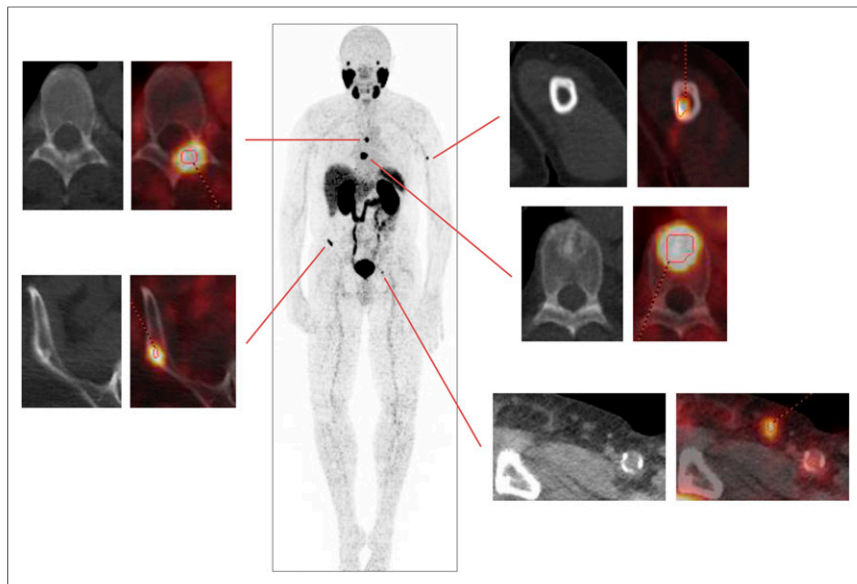


FIGURE 1. Volumetric assessment of whole-body tumor burden using ^{68}Ga -PSMA I&T PET. Maximum-intensity projection showing several metastases (central panel). Volume of each individual tumor lesion (left and right panels) is segmented and summed up for calculation of whole-body PSMA-TV. In this patient with a PSA level of 15.88 ng/mL, PSMA-TV is 4.8 cm³ and TL-PSMA is 96.89 cm³.

follow-up ^{68}Ga -PSMA I&T PET/CT scan. Relative changes in PSA levels were compared with relative changes in SUVs, PSMA-TV, and TL-PSMA.

Statistical Analysis

Categoric variables are presented with absolute and relative frequencies. Continuous variables are expressed as mean \pm SD and

range. Pearson correlation was used to explore the association of imaging findings with PSA levels. A 1-way ANOVA with a Tukey multiple-comparison test was performed to analyze the association between volumetric parameters and Gleason scores. Stepwise multiple-regression analysis was performed to identify independent variables for PSMA-TV and TL-PSMA. Statistical significance was established for *P* values of 0.05 or less. Statistical analysis was performed using GraphPad Prism (version 6.0 for Windows; GraphPad Software) or MedCalc (version 17.2; MedCalc Software).

RESULTS

The evaluation of ^{68}Ga -PSMA I&T PET/CT scans including assessment of PSMA-TV and TL-PSMA was feasible in all patients. Relevant patient characteristics are shown in Table 1.

^{68}Ga -PSMA I&T Imaging Findings and Volumetric Parameters

A total of 304 lesions were detected in 101 patients. A total of 202 lymph node metastases were found in 74 (73.3%) patients, 73 bone metastases in 31 (30.7%) patients, 17 local recurrences in 17 (16.8%) patients, and 12 other metastases in 6 (5.9%) patients. On average, 3.0 ± 2.6 lesions (range, 1–10) were found in an individual ^{68}Ga -PSMA I&T PET/CT-positive patient. Detailed data on PSMA-TV, TL-PSMA, and intensity of tracer uptake are shown in Table 2.

Serum PSA Levels Are Associated with Whole-Body PSMA-TV

Whole-body PSMA-TV demonstrated a statistically significant correlation with PSA levels ($r = 0.48$, $P < 0.0001$). The correlation was statistically significant for both well-differentiated tumors (Gleason 6, $r = 0.98$, $P < 0.0001$) and poorly differentiated tumors (Gleason ≥ 9 , $r = 0.53$, $P = 0.006$), but not for Gleason 7 and 8 tumors.

When whole-body PSMA-TV was analyzed using primary Gleason scores (Supplemental Fig. 1; supplemental materials are available at <http://jnm.snmjournals.org>), differences among PSMA-TV means were not statistically significant (1-way ANOVA, $P = 0.32$), meaning that metastatic TV did not depend on primary Gleason score. In multiple-regression analysis, PSA levels ($r_{\text{partial}} = 0.48$, $P < 0.0001$), but not initial Gleason score, were independently associated with PSMA-TV. The relation between whole-body PSMA-TV, PSA levels, and Gleason scores is illustrated in Figures 2 and 3.

Serum PSA Levels Are Associated with Whole-Body TL-PSMA

Whole-body TL-PSMA demonstrated a statistically significant correlation with PSA levels ($r = 0.52$, $P < 0.0001$). The correlation was statistically significant for both well-differentiated tumors (Gleason 6, $r = 0.98$, $P < 0.0001$) and poorly differentiated tumors (Gleason ≥ 9 , $r = 0.59$, $P = 0.002$), but not for Gleason 7 and 8 tumors.

TABLE 2

Volumetric ^{68}Ga -PSMA I&T PET Parameters (PSMA-TV and TL-PSMA) and Intensity of Tracer Uptake of Study Population

Parameter	Value	
	Per-lesion basis	Per-patient basis
^{68}Ga-PSMA I&T uptake intensity		
SUV _{max}		
Mean \pm SD	15.7 \pm 13.7	21.6 \pm 16.6
Range	1.7–92.3	2.6–92.3
SUV _{mean}		
Mean \pm SD	10.8 \pm 10.0	10.4 \pm 8.0
Range	1.1–66.9	2.0–42.8
^{68}Ga-PSMA I&T TV		
PSMA-TV (cm ³)		
Mean \pm SD	1.1 \pm 1.2	3.4 \pm 4.2
Range	0.1–10.2	0.1–21.6
TL-PSMA (cm ³)		
Mean \pm SD	11.0 \pm 18.2	33.2 \pm 51.9
Range	0.5–195.6	1.1–312.7

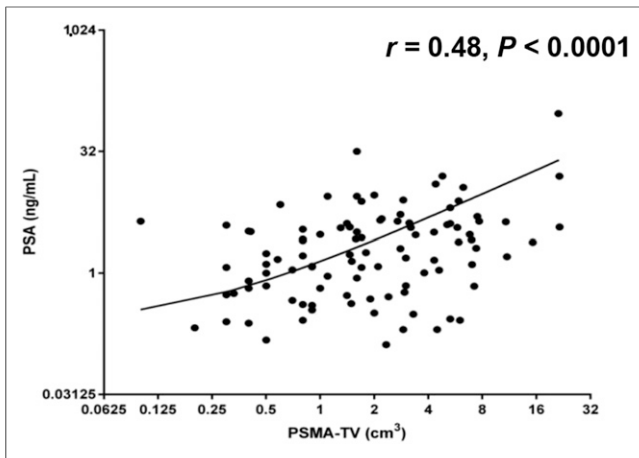


FIGURE 2. PSMA-TV for volumetric assessment of whole-body tumor burden using ^{68}Ga -PSMA I&T PET. PSMA-TV demonstrates significant correlation with PSA levels ($r = 0.48, P < 0.0001$).

When whole-body TL-PSMA was analyzed using primary Gleason scores (Supplemental Fig. 2), differences among TL-PSMA means were statistically significant (1-way ANOVA, $P = 0.01$), meaning that metastatic TL-PSMA depends on primary Gleason score. Specifically, TL-PSMA was significantly higher in patients with a Gleason score of 9 or more compared with Gleason 7 (56.2 ± 14.5 vs. $18.9 \pm 4.0, P = 0.002$). Differences among other Gleason scores were not statistically significant. In multiple-regression analysis, PSA ($r_{\text{partial}} = 0.57, P < 0.0001$) and initial Gleason score ($r_{\text{partial}} = 0.33, P < 0.001$) were independently associated with TL-PSMA. The relation between whole-body TL-PSMA, PSA levels, and Gleason scores is illustrated in Figures 4 and 5.

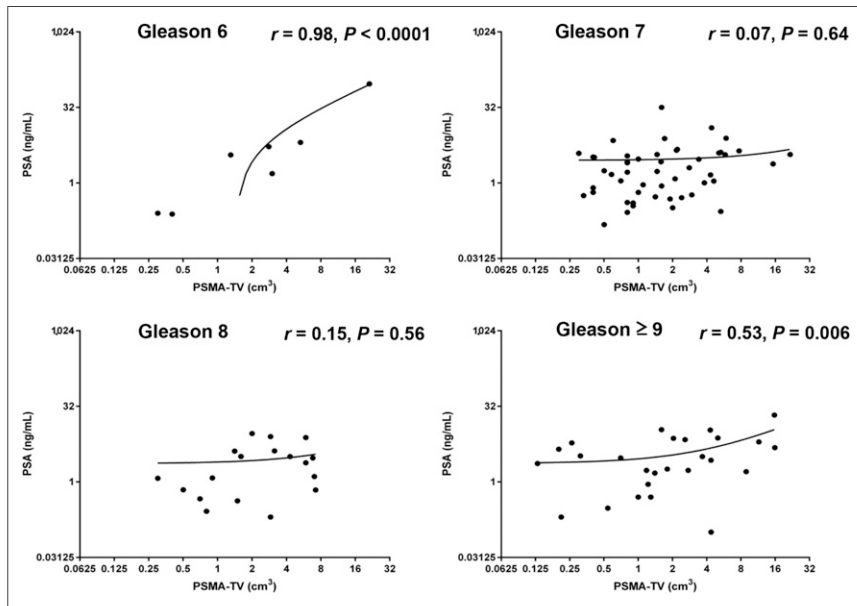


FIGURE 3. PSMA-TV for volumetric assessment of whole-body tumor burden using ^{68}Ga -PSMA I&T PET. In subgroup analysis, correlation was statistically significant for Gleason 6 and Gleason ≥ 9 tumors, but not for Gleason 7 and 8 tumors.

Serum PSA Levels Are Not Associated with SUVs

Neither SUV_{max} ($r = 0.12, P = 0.22$) nor average SUV_{mean} ($r = 0.8, P = 0.45$) demonstrated a significant correlation with PSA levels.

Preliminary Data of Volumetric Parameters for Treatment Monitoring

To support the hypothesis that single number volumetric whole-body parameters may be useful for disease monitoring, 10 patients who underwent a baseline and a follow-up ^{68}Ga -PSMA I&T PET/CT scan (6 patients after initiation of androgen-deprivation therapy [ADT], 1 of these with additional ^{223}Ra -dichloride therapy, 2 patients after salvage lymphadenectomy, and 2 patients under “watchful waiting” in the setting of rising PSA) were analyzed (Fig. 6). In 2 patients, PSA levels decreased at follow-up, whereas in 8 patients the PSA levels increased. Both whole-body PSMA-TV ($P = 0.02$) and whole-body TL-PSMA ($P = 0.02$) concordantly increased in all patients with increasing PSA levels and declined in all patients with declining PSA levels. Conversely, neither the change in SUV_{max} ($P = 1.0$) nor the change in SUV_{mean} ($P = 1.0$) concordantly paralleled changes in PSA levels, whereby SUVs increased in 1 patient with declining PSA levels and declined in 4 patients with rising PSA levels. Results of the correlation analysis between changes in ^{68}Ga -PSMA I&T PET parameters and changes in PSA levels are shown in Figure 7 and Supplemental Figure 3.

DISCUSSION

In the present study, we demonstrated that PSMA-TV and TL-PSMA may be used as quantitative imaging biomarkers in patients with prostate cancer and that these parameters may be applied for therapy monitoring. The use of volumetric parameters in ^{18}F -FDG PET has gained interest to predict treatment response and overall prognosis in oncologic patients. For instance, van

Rossum et al. demonstrated that the change in TLG after induction chemotherapy was predictive for a poor pathologic response in patients with esophageal adenocarcinoma (15). In another study, baseline MTV before chemotherapy for diffuse large B cell lymphoma was the only statistically significant predictor of progression-free survival at multivariate analysis (16). In prostate cancer, volumetric parameters have been evaluated in a small number of studies using radiotracers other than PSMA ligands (22,23). Incerti et al. assessed the value of ^{11}C -choline PET/CT in the context of radiation treatment of lymph node recurrence from prostate cancer and reported that MTV was significantly associated with the clinical relapse-free survival and biochemical relapse-free survival (22).

We have applied the concept of whole-body MTV or TLG assessment into the setting of PSMA imaging of prostate cancer. When the relationship between serum PSA levels and volumetric PET parameters was analyzed, a statistically significant correlation was observed with

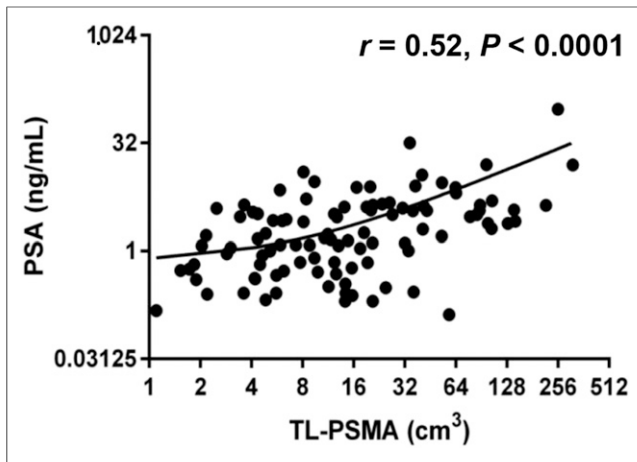


FIGURE 4. TL-PSMA for volumetric assessment of whole-body tumor burden using ^{68}Ga -PSMA I&T PET. TL-PSMA demonstrates significant correlation with PSA levels ($r = 0.52$, $P < 0.0001$).

both whole-body PSMA-TV ($r = 0.48$, $P < 0.0001$) and whole-body TL-PSMA ($r = 0.52$, $P < 0.0001$), demonstrating that the volumetric parameters were consistent with established biomarkers of metastatic tumor load. All patients had undergone radical prostatectomy before PET/CT-based restaging, and special attention was paid to exclude all patients with residual prostate tissue (e.g., after local cryotherapy), which might have influenced the correlation analysis between volumetric parameters and PSA. Previous studies found that high-grade tumors may produce less PSA per gram of tumor (24), and paradoxically low PSA levels in the context of poor differentiation may be observed, limiting the usefulness of PSA measurements (12). Volumetric PET parameters demonstrated a highly significant correlation with PSA ($P < 0.0001$), which was driven by Gleason 6 tumors (PSMA-TV, $r =$

0.98 , $P < 0.0001$) and Gleason ≥ 9 tumors (PSMA-TV, $r = 0.53$, $P = 0.006$). By contrast, no significant correlation was found between PSA levels and TV in Gleason 7 and Gleason 8 tumors. There is currently no model to fully explain this phenomenon. Other PET-derived parameters such as SUVs are not useful for assessment of tumor burden, because they characterize only the intensity of tracer uptake in individual lesions. Accordingly, neither SUV_{max} ($r = 0.12$, $P = 0.22$) nor SUV_{mean} ($r = 0.8$, $P = 0.45$) was associated with PSA levels in this study. Recently, novel biomarkers have been investigated for improved detection of prostate cancer. It would be interesting to explore the correlation of metastatic load on PET/CT and these biomarkers, for example, kallikreins (25).

Whole-body PSMA-TV was not significantly associated with primary Gleason scores ($P = 0.32$), as was to be expected. The size of metastases depends on other factors such as proliferation rate or previous treatment history. By contrast, whole-body TL-PSMA was independently associated with the initial Gleason score ($r_{\text{partial}} = 0.33$, $P < 0.001$). Besides volume, TL-PSMA also considers the degree of PSMA expression. In previous studies, high-level PSMA expression has been found in higher Gleason scores (26), providing an explanation for the correlation between Gleason score and TL-PSMA. However, the major determinant of TL-PSMA is also the patient's individual course of the disease.

Considering potential applications of volumetric PSMA PET imaging, the prediction of therapy response of internal-emitter therapy may be an interesting option. The metastatic cure probability has been demonstrated to depend on the tumor size and the intratumoral activity concentration in radionuclide therapy influencing the absorbed dose (27). TL-PSMA may be an ideal parameter to account for both lesion size and intralesional PSMA expression when predicting metastatic cure. Moreover, treatment planning based on the extent of tumor burden has recently gained prominence in metastatic prostate cancer therapy (28,29). Several clinical trials have used tumor burden for stratification of patients

into low- or high-volume disease. In a recent study that assessed whether ADT plus docetaxel would result in longer overall survival than ADT alone, the median overall survival was 17.0 mo longer in the combination group than in the ADT-alone group (49.2 vs. 32.2 mo) in the subgroup of patients with high-volume disease (28). In the absence of a sensitive imaging-derived biomarker, stratification was performed using suboptimal methods, for example, high volume was defined as the presence of visceral metastases or 4 bone lesions or more with 1 or more beyond the vertebral bodies and pelvis in the aforementioned study (28). In the Southwest Oncology Group trials, minimal disease was defined as disease confined to the spine, pelvic bones, or lymph nodes (29). These definitions can provide only an imprecise estimate of whole-body tumor burden. A more sophisticated approach using PSMA-TV or TL-PSMA may considerably refine stratification of patients, providing real volumetric parameters and a more accurate assessment of the tumor burden.

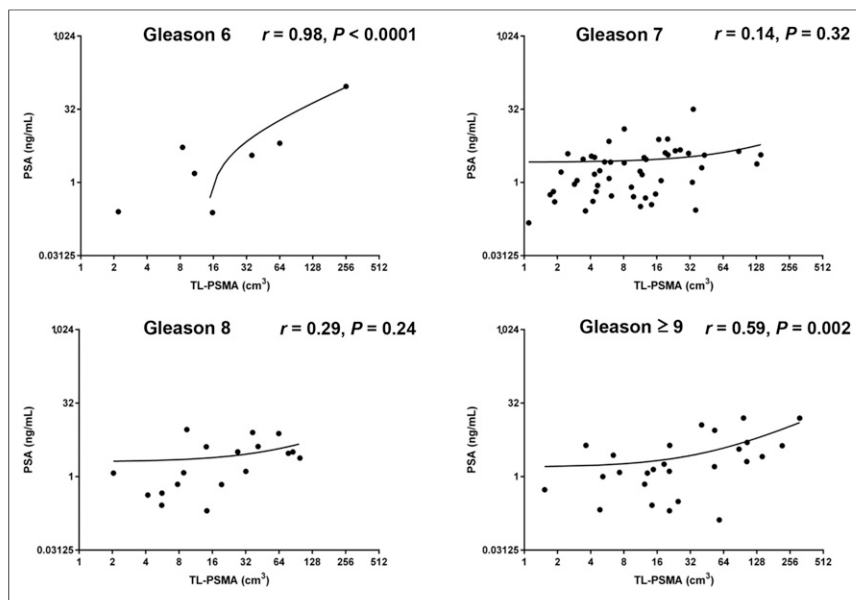


FIGURE 5. TL-PSMA for volumetric assessment of whole-body tumor burden using ^{68}Ga -PSMA I&T PET. In subgroup analysis, correlation was statistically significant for Gleason 6 and Gleason ≥ 9 tumors, but not for Gleason 7 and 8 tumors.

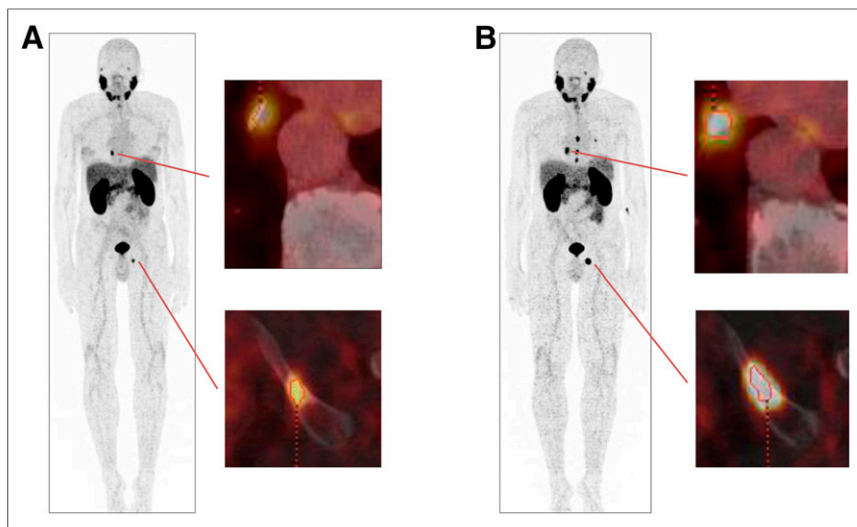


FIGURE 6. Volumetric assessment of whole-body tumor burden using ^{68}Ga -PSMA I&T PET for therapy monitoring. Baseline PET (A) and follow-up PET (B) 7 mo after initiation of ADT (new lesions are not displayed separately). Serum PSA level increased from 1.22 to 5.01 ng/mL. PSMA-TV concordantly increased from 0.9 to 7.5 cm^3 , and TL-PSMA increased from 7.29 to 104.46 cm^3 , respectively.

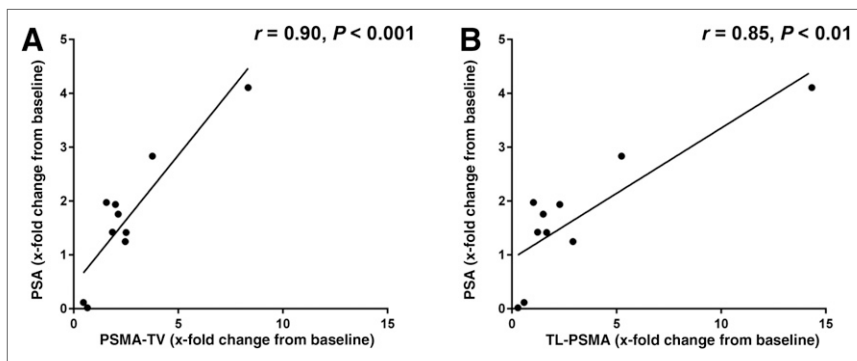


FIGURE 7. Graphical illustration of results of correlation analysis between changes of ^{68}Ga -PSMA I&T PET parameters and changes in PSA levels. Relative change in PSA level over time is significantly correlated with relative change of both PSMA-TV (A, $r = 0.90$, $P < 0.001$) and TL-PSMA (B, $r = 0.85$, $P < 0.01$).

Assessment of volumetric parameters was time- and labor-intensive in this cohort with metastatic prostate cancer, and we therefore restricted the analysis to patients with 10 or fewer metastases. Although our approach consisting of manual placement of volumes of interest may also be used in patients with more than 10 lesions, other technical approaches may facilitate the assessment of volumetric parameters in patients with extensive disease, for example, fully automated, SUV threshold-based whole-body segmentation techniques that allow for a rapid definition of whole-body tumor burden (14).

Some limitations of the present study should be acknowledged. First, the study was retrospective in nature. Second, we evaluated a single threshold for calculation of PSMA-TV and TL-PSMA. It is important to keep in mind that volumetric data generated by PET represent an estimate of the true volume. Although we experimentally determined that a threshold of 45% provided the best results using our imaging and reconstruction protocol, and have used this threshold in previous studies (9), further refinement using

different cutoff values, for example, 46% or 47%, may be beneficial. However, the observed correlations are robust and consistent with the literature. Moreover, the lesions chosen for the threshold assessment were representative of the total study population. The precise threshold used in this study may not be generalized to all types of acquisition protocols or reconstruction techniques but provides a proof of concept for volumetric assessment of prostate cancer lesions. Furthermore, ADT may alter PSMA expression by tumor cells and may potentially influence volumetric assessment based on an SUV_{max} threshold. Third, it would be desirable to obtain additional histopathologic specimens for assessment of the differentiation of metastatic lesions. After previous treatment, the initial Gleason score may not fully reflect the differentiation of metastases. However, this was not possible for both practical and ethical reasons. Finally, we demonstrated the feasibility of volumetric PSMA ligand PET and explored the relation of PSMA-TV and TL-PSMA with serum PSA levels. Future prospective studies will investigate the prognostic impact of these parameters in prostate cancer.

CONCLUSION

PSMA-derived volumetric parameters provide a quantitative imaging biomarker for whole-body tumor burden, capable of standardizing quantitative changes in PET imaging of patients with metastatic prostate cancer and of facilitating therapy monitoring. Volumetric assessment may allow better stratification of patients into low- and high-volume metastatic disease in clinical trials. Further evaluation will determine the potential prognostic impact of these PET-based parameters in metastatic prostate cancer.

DISCLOSURE

Prof. Dr. Hans-Jürgen Wester is a shareholder of Scintomics. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENT

We thank James T. Thackeray, PhD, for his thorough revision and language editing of the manuscript.

REFERENCES

- Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid ^{68}Ga -PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med.* 2015;56:668–674.

2. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the ⁶⁸Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:197–209.
3. Derlin T, Weirich D, von Klot C, et al. ⁶⁸Ga-PSMA I&T PET/CT for assessment of prostate cancer: evaluation of image quality after forced diuresis and delayed imaging. *Eur Radiol*. 2016;26:4345–4353.
4. Eiber M, Weirich G, Holzapfel K, et al. Simultaneous ⁶⁸Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. *Eur Urol*. 2016;70:829–836.
5. Herrmann K, Bluemel C, Weineisen M, et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. *J Nucl Med*. 2015;56:855–861.
6. Weineisen M, Schottelius M, Simecek J, et al. ⁶⁸Ga- and ¹⁷⁷Lu-labeled PSMA I&T: optimization of a PSMA-targeted theranostic concept and first proof-of-concept human studies. *J Nucl Med*. 2015;56:1169–1176.
7. Dietlein F, Kobe C, Neubauer S, et al. PSA-stratified performance of ¹⁸F- and ⁶⁸Ga-labeled tracers in PSMA-PET imaging of patients with biochemical recurrence of prostate cancer. *J Nucl Med*. 2017;58:947–952.
8. Berliner C, Tienken M, Frenzel T, et al. Detection rate of PET/CT in patients with biochemical relapse of prostate cancer using [⁶⁸Ga]PSMA I&T and comparison with published data of [⁶⁸Ga]PSMA HBED-CC. *Eur J Nucl Med Mol Imaging*. 2017;44:670–677.
9. Schmuck S, Nordlohne S, von Klot CA, et al. Comparison of standard and delayed imaging to improve the detection rate of [⁶⁸Ga]PSMA I&T PET/CT in patients with biochemical recurrence or prostate-specific antigen persistence after primary therapy for prostate cancer. *Eur J Nucl Med Mol Imaging*. 2017;44:960–968.
10. Schmuck S, Mamach M, Wilke F, et al. Multiple time-point ⁶⁸Ga-PSMA I&T PET/CT for characterization of primary prostate cancer: value of early dynamic and delayed imaging. *Clin Nucl Med*. 2017;42:e286–e293.
11. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenez M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? *J Urol*. 2004;172:1297–1301.
12. Sandblom G, Ladjevardi S, Garmo H, Varenhorst E. The impact of prostate-specific antigen level at diagnosis on the relative survival of 28,531 men with localized carcinoma of the prostate. *Cancer*. 2008;112:813–819.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
14. Salamon J, Papp L, Tóth Z, et al. Nerve sheath tumors in neurofibromatosis type 1: assessment of whole-body metabolic tumor burden using F-18-FDG PET/CT. *PLoS One*. 2015;10:e0143305.
15. van Rossum PS, Fried DV, Zhang L, et al. The value of ¹⁸F-FDG PET before and after induction chemotherapy for the early prediction of a poor pathologic response to subsequent preoperative chemoradiotherapy in oesophageal adenocarcinoma. *Eur J Nucl Med Mol Imaging*. 2017;44:71–80.
16. Mikhaeel NG, Smith D, Dunn JT, et al. Combination of baseline metabolic tumour volume and early response on PET/CT improves progression-free survival prediction in DLBCL. *Eur J Nucl Med Mol Imaging*. 2016;43:1209–1219.
17. Husby JA, Reitan BC, Biermann M, et al. Metabolic tumor volume on ¹⁸F-FDG PET/CT improves preoperative identification of high-risk endometrial carcinoma patients. *J Nucl Med*. 2015;56:1191–1198.
18. Ulmert D, Kaboth R, Fox JJ, et al. A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the Bone Scan Index. *Eur Urol*. 2012;62:78–84.
19. Poulsen MH, Rasmussen J, Edenbrandt L, et al. Bone scan index predicts outcome in patients with metastatic hormone-sensitive prostate cancer. *BJU Int*. 2016;117:748–753.
20. Martin R, Jüttler S, Müller M, Wester HJ. Cationic eluate pretreatment for automated synthesis of [⁶⁸Ga]CPCR4.2. *Nucl Med Biol*. 2014;41:84–89.
21. Rauscher I, Maurer T, Beer AJ, et al. Value of ⁶⁸Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. *J Nucl Med*. 2016;57:1713–1719.
22. Incerti E, Fodor A, Mapelli P, et al. Radiation treatment of lymph node recurrence from prostate cancer: is ¹¹C-choline PET/CT predictive of survival outcomes? *J Nucl Med*. 2015;56:1836–1842.
23. Oprea-Lager DE, Kramer G, van de Ven PM, et al. Repeatability of quantitative ¹⁸F-fluoromethylcholine PET/CT studies in prostate cancer. *J Nucl Med*. 2016;57:721–727.
24. Partin AW, Carter HB, Chan DW, et al. Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. *J Urol*. 1990;143:747–752.
25. Nordström T, Vickers A, Assel M, Lilja H, Grönberg H, Eklund M. Comparison between the four-kallikrein panel and prostate health index for predicting prostate cancer. *Eur Urol*. 2015;68:139–146.
26. Minner S, Wittmer C, Graefen M, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. *Prostate*. 2011;71:281–288.
27. Bernhardt P, Ahlman H, Forsell-Aronsson E. Modelling of metastatic cure after radionuclide therapy: influence of tumor distribution, cross-irradiation, and variable activity concentration. *Med Phys*. 2004;31:2628–2635.
28. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373:737–746.
29. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*. 2013;368:1314–1325.