The Impact of PSMA PET–Based Eligibility Criteria Used in the Prospective Phase II TheraP Trial in Metastatic Castration-Resistant Prostate Cancer Patients Undergoing Prostate-Specific Membrane Antigen–Targeted Radioligand Therapy

Amir Karimzadeh[1,2], Matthias Heck[3], Robert Tauber[3], Esteban Solaris[1], Stephan Nekolla[1], Karina Knorr[1], Bernhard Haller[4], Calogero D'Alessandria[1], Wolfgang A. Weber[1], Matthias Eiber*[1], and Isabel Rauscher*[1]

[1]*Department of Nuclear Medicine, School of Medicine, Technical University of Munich, Munich, Germany;* [2]*Department of Diagnostic and Interventional Radiology and Nuclear Medicine, University Medical Center Hamburg–Eppendorf, Hamburg, Germany;* [3]*Department of Urology, School of Medicine, Technical University of Munich, Munich, Germany; and* [4]*Institute of AI and Informatics in Medicine, School of Medicine, Technical University of Munich, Munich, Germany*

Prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) has shown encouraging results for treatment of metastatic castration-resistant prostate cancer (mCRPC) in the prospective, multicenter, randomized phase II TheraP study. The inclusion criteria for that study comprised a pretherapeutic ^{68}Ga-PSMA-11 PET scan showing sufficient tumor uptake using a predefined threshold and the absence of ^{18}F-FDG–positive, PSMA ligand–negative tumor lesions. However, the prognostic value of these PET-based inclusion criteria remains unclear. Therefore, we evaluated the outcome of mCRPC patients treated with PSMA RLT using TheraP as well as other TheraP-based PET inclusion criteria. **Methods:** First, patients were dichotomized into 2 groups whose PSMA PET scans did (TheraP contrast-enhanced PSMA [cePSMA] PET–positive) or did not (TheraP cePSMA PET–negative) fulfill the inclusion criteria of TheraP. Notably, unlike in TheraP, ^{18}F-FDG PET was not performed on our patients. Prostate-specific antigen (PSA) response (PSA decline ≥ 50% from baseline), PSA progression-free survival, and overall survival (OS) were compared. Additionally, patients were further dichotomized according to predefined SUV_{max} thresholds different from those used in TheraP to analyze their potential impact on outcome as well. **Results:** In total, 107 mCRPC patients were included in this analysis (TheraP cePSMA PET–positive, $n = 77$; TheraP cePSMA PET–negative, $n = 30$). PSA response rates were higher in TheraP cePSMA PET–positive patients than in TheraP cePSMA PET–negative patients (54.5% vs. 20%, respectively; $P = 0.0012$). The median PSA progression-free survival ($P = 0.007$) and OS ($P = 0.0007$) of patients were significantly longer in the TheraP cePSMA PET–positive group than in the TheraP cePSMA PET–negative group. Moreover, being in the TheraP cePSMA PET–positive group was identified as a significant prognosticator of longer OS ($P = 0.003$). The application of different SUV_{max} thresholds for a single hottest lesion demonstrated no influence on outcome in patients eligible for PSMA RLT. **Conclusion:** Patient selection for PSMA RLT according to the inclusion criteria of TheraP led to a better treatment response and outcome in our preselected patient cohort. However, a relevant number of patients not fulfilling these criteria also showed substantial rates of response.

Key Words: metastatic castration-resistant prostate cancer; mCRPC; TheraP; ^{68}Ga-PSMA-11 PET; prostate-specific membrane antigen targeted radioligand therapy; PSMA RLT

J Nucl Med 2023; 64:1252–1258
DOI: 10.2967/jnumed.122.265346

In patients with metastatic castration-resistant prostate cancer (mCRPC), prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) has emerged as a promising option with favorable efficacy and low toxicity and was recently approved by the Food and Drug Administration and the European Medicines Agency (*1–4*). Patients who received prior treatment usually undergo PET imaging (e.g., using ^{68}Ga-PSMA-11) to assess for sufficient PSMA ligand uptake (*5*). To date, the criteria used to select patients are inconsistent in clinical use and even differ between prospective clinical trials (*6*).

Recently, the prospective, multicenter, randomized phase II TheraP study was published comparing ^{177}Lu-PSMA-617 with cabazitaxel in 200 mCRPC patients (*7*). It reported a significantly higher treatment response and less toxicity in patients receiving ^{177}Lu-PSMA-617. This trial used strict PSMA ligand PET–based selection criteria requiring high ^{68}Ga-PSMA-11 tumor uptake with an SUV_{max} of at least 20 for at least 1 metastatic site, an SUV_{max} of greater than 10 for all other measurable (diameter, ≥10 mm) lesions, and absence of ^{18}F-FDG–positive, PSMA ligand–negative tumor lesions (*7*). ^{177}Lu-PSMA-I&T is another PSMA ligand showing promising results for therapy of mCRCP and is currently being explored in a prospective, multicenter, randomized phase III trial on mCRPC prior chemotherapy (SPLASH, NCT04647526) after second-line hormonal treatment (*3,8*). However, with the first results being expected in 2023, the PSMA PET avidity criteria required in this trial are so far unknown and cannot be addressed. High tumor uptake of ^{68}Ga-PSMA-11 correlates with higher tumor radiation doses (*9*) and—despite not being proven for PSMA RLT—yields

Received Dec. 19, 2022; revision accepted Mar. 24, 2023.
For correspondence or reprints, contact Amir Karimzadeh (amir.karimzadeh@uke.de).
*Contributed equally to this work.
Published online Jun. 8, 2023.

TABLE 1
Baseline Patient Characteristics

Characteristic	Data
No. of patients	107
Age (y)	73 (66–76)
PSA (ng/mL)	115 (19–324)
Lactate dehydrogenase (U/L)	266 (217–350)
Alkaline phosphatase (U/L)	101 (72–229)
Hemoglobin (g/dL)	11.5 (10.1–12.4)
Prior systemic therapies for mCRPC	
Docetaxel	82
Cabazitaxel	20
Abiraterone	87
Enzalutamide	63
^{223}Ra	19
Previous chemotherapy	82
Site of metastasis	
Lymph node, overall	87
Lymph node only (N1+/M1a)	7
Bone overall	97
Bone (M1b, without visceral metastases)	71
Visceral, overall (M1c)	31
Liver	10
Lung	14
Adrenal	10

Qualitative data are number and percentage; continuous data are median and interquartile range (n = 107).

promise of better treatment effects. Therefore, following the theranostic paradigm, it seems reasonable to limit RLT to patients with high ^{68}Ga-PSMA-11 tumor uptake and avoid including patients with a lower chance of response but still at risk for side effects. However, it remains unclear how well the selected SUV_{max} thresholds separate patients who do benefit from RLT from those do not, as biologic differences in the tumor might also play a substantial role.

Thus, the aim of this retrospective analysis was to evaluate the prognostic value of predefined SUV_{max}-based thresholds, including those applied in TheraP for the outcome of PSMA RLT. Outcome was measured by a prostate-specific antigen (PSA) decline of at least 50% from baseline, PSA progression-free survival (PFS), and overall survival (OS). Of note, the investigation included our large cohort of mCRPC patients previously treated with RLT using less restrictive criteria than in TheraP and therefore also encompasses patients who would not have been selected for RLT in this trial.

MATERIALS AND METHODS

Patients and ^{177}Lu-PSMA-I&T RLT

From our institutional database of patients who underwent PSMA RLT using ^{177}Lu-PSMA-I&T from December 2014 to July 2020 at the Department of Nuclear Medicine, School of Medicine, Technical University of Munich, 120 patients with ^{68}Ga-PSMA-11 PET/CT imaging before treatment were screened, and 107 consecutive patients with PSMA PET imaging performed at our institution were selected. This patient population includes 73 patients for whom the safety and antitumor effect of PSMA RLT, but not the prognostic value of pretherapeutic ^{68}Ga-PSMA-11 PET, have already been reported by Heck et al. (*3*). All patients had previously received second-line hormonal therapy with abiraterone or enzalutamide as well as chemotherapy or were unfit for chemotherapy. The patient characteristics are shown in Table 1. Before treatment, uptake in tumor lesions was confirmed by ^{68}Ga-PSMA-11 PET imaging, and patients needed to present with lesions showing PSMA ligand uptake at least as high as liver background uptake. ^{177}Lu-PSMA-I&T was synthesized and radiolabeled as reported by Weineisen et al. (*10*). ^{177}Lu-PSMA-I&T was prepared according to good manufacturing practices and the German Medicinal Products Act (Arzneimittelgesetz §13 2b). In total, 444 cycles of PSMA RLT with a median of 4 cycles per patient (range, 2–20 cycles) were applied. Treatment was discontinued in patients with radiographic or clinical signs of progression or the appearance of severe toxicity according to the investigator. Patients received an intravenous treatment using a standard activity of 7.4 GBq of ^{177}Lu-PSMA-I&T every 4–10 wk (median, 6 wk), which could be slightly adapted on the basis of, for example, lab test results and tumor burden. All patients gave written informed consent and were treated under the conditions of Declaration of Helsinki article 37, "Unproven Interventions in Clinical Practice." The retrospective analysis was approved by the local ethics committee under reference number 115/18 S.

Image Analysis and Definition of PET Eligibility

^{68}Ga-PSMA-11 was synthesized according to Eder et al. (*11*). ^{68}Ga-PSMA-11 was given to patients via an intravenous bolus followed by an intravenous injection of diuretic (furosemide). The PET acquisition began about 60 min after injection. All patients were examined on a Biograph mCT scanner (Siemens Medical Solutions). A diagnostic CT scan was initially performed in the portal venous phase 80 s after

TABLE 2
PET-Based Eligibility Criteria

Criterion	PET-based eligibility in TheraP using ^{68}Ga-PSMA-11 and ^{18}F-FDG PET (*7*)	Institutional PET-based eligibility criteria using ^{68}Ga-PSMA-11 and contrast-enhanced CT
Inclusion	PSMA-positive disease with at least SUV_{max} of 20 at site of disease; SUV_{max} greater than 10 at all other sites of measurable (diameter, ≥10 mm) metastatic disease	PSMA ligand uptake at least as high as liver background uptake in most metastatic lesions
Exclusion	Metastatic site of disease with discordant ^{18}F-FDG–positive and ^{68}Ga-PSMA-11–negative findings	Any negative visceral metastases (>1 cm) or relevant fraction (~>25%) of soft-tissue lesions in contrast-enhanced CT with PSMA ligand uptake lower than liver uptake

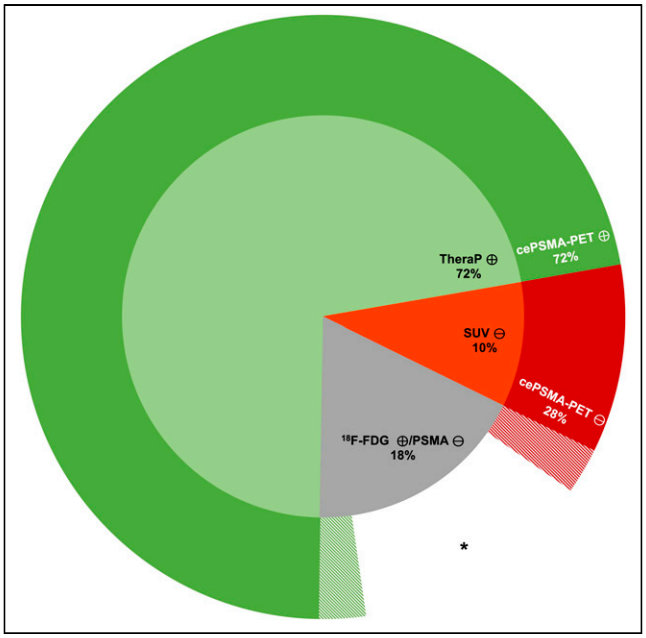

FIGURE 1. Comparison of PET eligibility criteria used in TheraP (inner pie chart) and our retrospective stratification of patients (outer pie chart). In inner pie chart, green fill is patients who fulfilled PET eligibility criteria according to TheraP (TheraP–positive, 72%), gray fill is patients who were excluded because of discordant ^{18}F-FDG–positive, PSMA-negative metastatic disease (18%), and red fill is patients who were not included because of low uptake on ^{68}Ga-PSMA-11 PET/CT (SUV_{max}-negative, 10%). In outer pie chart (not drawn to scale), green is patients who retrospectively fulfilled inclusion criteria from TheraP (TheraP cePSMA PET–positive, 72%), and red is patients who retrospectively did not fulfill PSMA ligand PET-based SUV_{max} inclusion criteria (TheraP cePSMA PET–negative, 28%). Asterisk in gap represents patient cohort that was excluded from TheraP on basis of ^{18}F-FDG–positive, PSMA-negative disease and was also not treated with PSMA RLT at our institution because of PSMA-negative visceral or soft-tissue lesions. Hatched areas represent patients in our cohort who were treated with PSMA RLT but might have been excluded from TheraP because of ^{18}F-FDG–positive, PSMA-negative bone disease. ⊕ = positive; ⊖ = negative.

intravenous injection of an iodinated contrast agent (Imeron 300; Bracco Imaging) and was followed by the PET scan. All patients received a diluted oral contrast agent (300 mg of Telebrix; Guerbet). The PET scans were acquired in 3-dimensional mode with an acquisition time of 3–4 min per bed position or 1.1–1.5 mm/s using flow technique. Emission data were corrected for randoms, dead time, scatter, and attenuation and were reconstructed iteratively using ordered-subsets expectation maximization (4 iterations, 8 subsets) followed by a postreconstruction smoothing gaussian filter (5 mm in full width at half maximum). All patients were assessed as to whether they fulfilled the SUV_{max}-based criteria for ^{68}Ga-PSMA-11 uptake of TheraP (TheraP contrast-enhanced PSMA [cePSMA] PET–positive vs. TheraP cePSMA PET–negative). The criteria from TheraP used for this analysis are shown in Table 2. In an additional analysis, we further explored the impact of the SUV_{max} threshold of 20 required to be fulfilled by at least 1 lesion in TheraP. For this analysis, exploratory thresholds between an SUV_{max} of 10 and an SUV_{max} of 50 were used, and the patients were restratified. The requirement of the SUV_{max}-based TheraP criteria of an SUV_{max} of at least 10 at all other sites of measurable (diameter, ≥10 mm) metastatic disease remained unchanged for this analysis. To determine the SUV_{max} of the tumor lesions, all were semiautomatically segmented using a predefined threshold and annotated regarding their malignancy (benign vs. malignant) and anatomic location (tissue type, organ) using the prototype software as described by Capobianco et al. (*12*). Our approach consisted of the following steps: first, all PSMA-avid foci with an SUV_{max} of at least 10 were automatically preselected, and foci with a PET volume smaller than 0.5 mL were discarded. Second, missed foci or foci falsely marked as physiologic were manually adjusted, if needed. Third, after the semiautomatic preselection of appropriate PSMA-avid foci, all ^{68}Ga-PSMA-11 PET/CT scans were reread to assess whether they fulfilled the requirement of measurable metastatic disease.

Notably, in comparison to TheraP, our patients do not undergo ^{18}F-FDG PET before ^{177}Lu-PSMA RLT. However, our institutional PET eligibility criteria (Table 2) require the use of contrast-enhanced CT, which, in comparison to ^{68}Ga-PSMA-11 PET, can identify PSMA ligand–negative visceral and soft-tissue lesions. With this approach, only potential nonsclerotic PSMA-negative and ^{18}F-FDG–positive disease might be missed.

Clinical Parameters, PSA Response, and PSA Progression

The following pretherapeutic parameters were collected and correlated with patient outcome: age, alkaline phosphatase, lactate dehydrogenase, hemoglobin, PSA, prior systemic therapies (including abiraterone, enzalutamide, first- and second-line chemotherapy, and ^{223}Ra), lymph node–only metastases (N+/M1a), and visceral metastases (M1c). According to Prostate Cancer Clinical Trials Working Group 3, a PSA decline of at least 50% from baseline was defined as a PSA response (*12*). PSA progression was defined as either a PSA increase of at least 25% and at least 2 ng/mL above the nadir after an initial PSA decline or a PSA increase of at least 25% and at least 2 ng/mL from baseline in cases with no PSA decline (*13*).

Statistical Analysis

The primary outcome measures were PSA response, PSA PFS, and OS. The Kaplan–Meier method was used to estimate event time

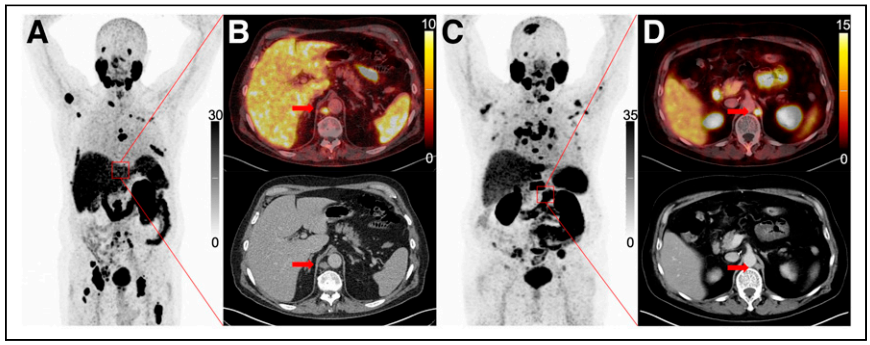

FIGURE 2. Examples of ^{68}Ga-PSMA-11 PET/CT in mCRPC patients. (A and B) Maximum-intensity projection (A) and PSMA ligand PET/CT (B, top) and corresponding CT dataset (B, bottom) in 67-y-old patient from TheraP cePSMA PET–negative group with bone and lymph node metastases presenting with retrocrural lymph node metastasis with short-axis diameter of 14 mm and SUV_{max} of 8.1 (arrows). (C and D) Maximum-intensity projection (C) and PSMA ligand PET/CT (D, top) with corresponding CT dataset (D, bottom) in 74-y-old patient from TheraP cePSMA PET–positive group with bone and lymph node metastases presenting with retrocrural lymph node metastasis with short-axis diameter of 11 mm and SUV_{max} of 10.8 (arrows). PSA PFS and OS were 11 wk and 8 mo, respectively, in patient shown in A and B and 45 wk and 45 mo, respectively, in patient shown in C and D.

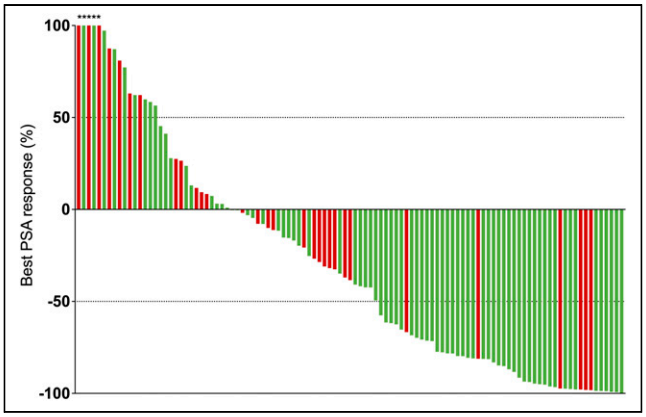

FIGURE 3. Waterfall plot showing response to treatment as measured by serum PSA. Color-coded best PSA response is defined as smallest increase or greatest decrease in PSA from baseline. Green indicates patients who fulfilled PET eligibility criteria (TheraP cePSMA PET–positive, $n = 77$). Red indicates patients who did not fulfill TheraP PET-based inclusion criteria (TheraP cePSMA PET–negative, $n = 30$). Asterisks indicate patients with increase of more than 100% in best PSA response.

distributions, and log-rank tests were used for group comparisons. The frequencies of PSA response between the cePSMA PET–positive and cePSMA PET–negative groups within each SUV_{max} threshold group were compared using χ^2 tests. Univariate and multivariate Cox regression analyses were performed to determine the association of pretherapeutic parameters with PSA PFS and OS. The corresponding hazard ratios (HRs) and 95% CIs are presented. A P value of less than 0.05 was considered statistically significant.

χ^2 tests, Kaplan–Meier estimation, and log-rank tests were performed using Prism, version 8.4.3 (GraphPad Software), for Mac (Apple). Uni- and multivariate Cox regression analyses were performed using SPSS Statistics, version 25.0. (IBM Corp.), for Windows (Microsoft).

RESULTS

In total, 107 patients were analyzed. The median time on treatment was 4 mo (range, 1–57 mo). At baseline, lymph node, bone, and visceral metastases were present in 87 (81.3%), 97 (90.7%), and 31 (29.0%) patients, respectively. The median follow-up time was 11 mo (range, 1–63 mo). Forty-eight (44.9%) patients achieved a PSA response after PSMA-targeted RLT. Median OS and PSA PFS were 14.0 mo (95% CI, 11.0–17.0 mo) and 17.6 wk (95% CI, 14.6–29.7 wk), respectively. At the time of analysis, 88 patients showed PSA progression and 97 had died.

Clinical Outcome of TheraP cePSMA PET–Positive and TheraP cePSMA PET–Negative Patients

Seventy-seven (72%) patients were classified as TheraP cePSMA PET–positive, and 30 patients were classified as TheraP cePSMA PET–negative (28%; 9 patients with no metastatic lesion with an $SUV_{max} \geq 20$, and 21 patients with ≥1 measurable metastatic lesion with an $SUV_{max} < 10$), who would not have been treated in TheraP on the basis of PSMA PET SUV_{max} criteria. Visceral metastases were present in 20 (26%) and 11 (37%) patients classified as TheraP cePSMA PET–positive and TheraP cePSMA PET–negative, respectively. Figure 1 compares the PET eligibility criteria used in TheraP with the retrospective stratification of patients treated in our compassionate-use program. Figures 2A–2D show an example of a TheraP cePSMA PET–positive patient and a TheraP cePSMA PET–negative patient.

PSA response was achieved by 54.5% ($n = 42$) and 20% ($n = 6$) of patients in the TheraP cePSMA PET–positive and TheraP cePSMA PET–negative groups, respectively ($P = 0.0012$). A PSA waterfall plot (Fig. 3) shows the correlation between TheraP SUV_{max} criteria and the best PSA response. The median PSA PFS and OS were 6.0 versus 3.2 mo, respectively (HR, 0.5; 95% CI, 0.3–0.8; $P = 0.007$; Fig. 4A), for the TheraP cePSMA PET–positive group and 15.0 versus 10.0 mo, respectively (HR, 0.4; 95% CI, 0.2–0.7; $P = 0.0007$; Fig. 4B) for the TheraP cePSMA PET–negative group.

Both univariate and multivariate Cox regression analyses indicated that a TheraP cePSMA PET–positive status is a significant positive prognosticator for OS ($P = 0.001$ and $P = 0.003$ for uni- and multivariate analysis, respectively; Table 3). On univariate analysis, further parameters associated with worse OS were rising levels of lactate dehydrogenase and PSA, decreasing levels of hemoglobin, and the presence of visceral metastases at baseline PET (Table 3). In the multivariate Cox regression model, only rising lactate dehydrogenase, decreasing hemoglobin, and the presence of visceral metastases remained independent predictors of poor OS apart from the TheraP cePSMA PET–positive status (Table 3).

Correlation Between Adapted SUV Thresholds for the Hottest Lesion on Clinical Outcome

When adjusting the SUV_{max} threshold required for at least 1 lesion without other changes in the PSMA ligand PET–based stratification, we obtained the following numbers of patients in the respective cePSMA PET–positive groups: 78 for an SUV_{max} of more than 10 or 15, 72 for an SUV_{max} of more than 25, 63 for an SUV_{max} of more than 30, 56 for an SUV_{max} of more than 35, 51 for an SUV_{max} of more than 40, and 47 for an SUV_{max} of more than 45 or 50 (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

The results on the PSA response, PSA PFS, and OS of the exploratory cePSMA PET–positive and cePSMA PET–negative groups using SUV_{max} thresholds of between 10 and 50 are presented in Supplemental Table 1. PSA responses significantly differed between the cePSMA PET–positive and cePSMA PET–negative groups when the threshold SUV_{max} for the hottest lesions was between 10 and 35 (all $P < 0.05$).

Further, the relative risk of death for the exploratory cePSMA PET–positive group showed a decreasing trend from a high to low adjusted SUV_{max}. It was lowest for an SUV_{max} of 20 (HR, 0.4; 95% CI, 0.3–0.9),

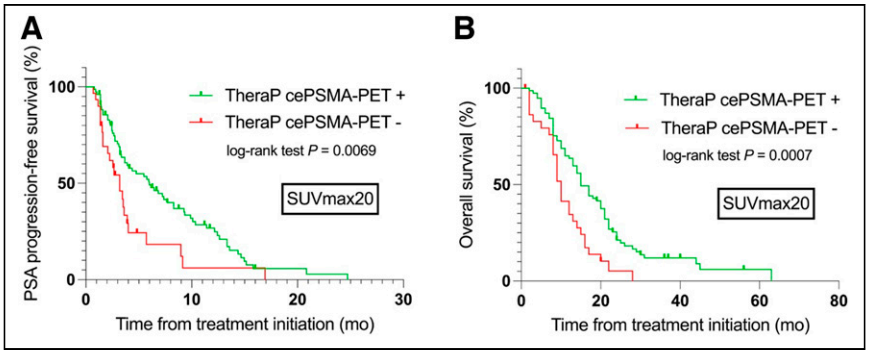

FIGURE 4. Kaplan–Meier survival curves for PSA PFS (A) and OS (B) in TheraP cePSMA PET–positive and TheraP cePSMA PET–negative patients.

TABLE 3
Uni- and Multivariate Cox Regression Analysis

Parameter	Patients (*n*)	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
TheraP criteria	107						
TheraP cePSMA PET–negative	30	Reference					
TheraP cePSMA PET–positive	77	0.5	0.3–0.8	0.001*	0.5	0.3–0.8	0.003*
Visceral metastases	107						
No		Reference					
Yes		1.7	1.2–2.6	0.02*	2.2	1.3–.2.7	0.005*
Lymph node only	107						
No		Reference					
Yes		0.4	0.2–1.1	0.07	0.6	0.2–1.6	0.3
Previous abiraterone	107						
No		Reference					
Yes		1.1	0.7–1.9	0.7	1.5	0.9–2.7	0.2
Previous enzalutamide	107						
No		Reference					
Yes		0.9	0.6–1.4	0.7	0.7	0.5–1.1	0.2
Previous ^{223}Ra	107						
No		Reference					
Yes		0.9	0.5–1.5	0.7	0.7	0.4–1.2	0.2
Previous chemotherapy	107						
Yes		Reference					
No		0.7	0.5–1.2	0.2	1.3	0.7–2.5	0.3
Age, risk change with 10 y increase	107						
Continuous		1.0	0.8–1.4	0.9	1.1	0.8–1.5	0.7
PSA, risk change with 50 ng/mL increase	107						
Continuous		1.0	1.0–1.0	0.02*	1.0	1.0–1.0	0.5
Hemoglobin (g/dL)	107						
Continuous		0.8	0.7–0.8	<0.0001*	0.7	0.6–0.9	<0.001*
AP, risk change with 50 U/L increase	107						
Continuous		1.0	1.0–1.0	0.05	1.0	1.0–1.1	0.9
LDH, risk change with 50 U/L increase	107						
Continuous		1.0	1.0–1.1	<0.0001*	1.1	1.0–1.1	0.03*

*Statistically significant.
AP = alkaline phosphatase; LDH = lactate dehydrogenase.

followed by an SUV_{max} of 10, 15, 25, and 30 (HR, 0.5; 95% CI, 0.3–0.8 each) (Supplemental Table 1). OS significantly differed between the cePSMA PET–positive and cePSMA PET–negative groups with an exploratory SUV_{max} of between 10 and 35 (all $P < 0.05$; Figs. 5A–5D).

The different exploratory SUV_{max} thresholds had no substantial effect on PSA response (range, 52.8%–55.6%) or median OS (range, 15.0–18.5 mo) in the group of cePSMA PET–positive patients. In the different exploratory cePSMA PET–negative groups, PSA response (range, 17.2%–38.3%) and median OS (range, 9.5–12.0 mo) declined in lower SUV_{max} thresholds (Supplemental Table 1).

DISCUSSION

Our retrospective analysis indicates that quantitative thresholds for PSMA ligand PET used in TheraP are predictive for response in patients treated with ^{177}Lu-PSMA RLT selected on the basis of visual ^{68}Ga-PSMA-11 uptake. Patients who fulfilled these criteria showed higher rates of maximum PSA response (54.5% vs. 20%, $P = 0.0012$), significantly longer PSA PFS (median, 6.0 vs. 3.2 mo, $P = 0.007$), and OS (median, 15.0 vs. 10.0 mo, $P = 0.0007$). Further, multivariate Cox regression analysis identified PSMA ligand PET–based criteria from TheraP (TheraP cePSMA PET–positive) as a new prognosticator for outcome in addition to known variables. In an additional exploratory analysis, adjustment of the

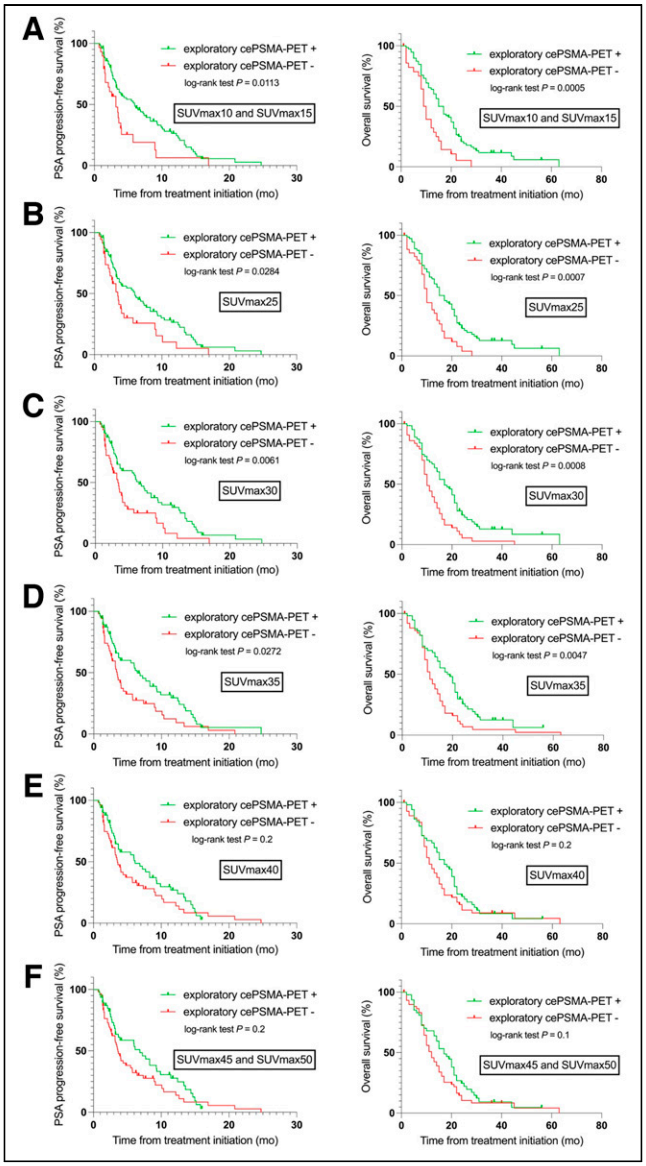

FIGURE 5. Kaplan–Meier survival curves for PSA PFS and OS in exploratory cePSMA PET–positive and exploratory cePSMA PET–negative patients stratified according to presence of PSMA-positive disease with SUV_{max} of at least 10 and 15 (A), 25 (B), 30 (C), 35 (D), 40 (E), and 45 and 50 (E).

SUV_{max} threshold required for the hottest lesion did not further select for higher response in the group fulfilling these criteria.

In TheraP, a maximum PSA decline of at least 50% was achieved in 66% of patients receiving ^{177}Lu-PSMA RLT, compared with 54.5% in our TheraP cePSMA PET–positive cohort. The corresponding OS in TheraP patients was 19.1 mo, compared with 15.0 mo in our TheraP cePSMA PET–positive cohort (*14*). The slight shift toward a lower PSA response rate and shorter OS in our analysis might be explained by the more advanced disease stage in our TheraP cePSMA PET–positive cohort (visceral metastases in 26% of TheraP cePSMA PET–positive patients [$n = 20$] vs. 7% in TheraP patients [$n = 7$]), given the known negative association of visceral metastases with outcome (*15*). Another possible contributor might be the inclusion of patients with nonsclerotic PSMA-negative and ^{18}F-FDG–positive bone disease in our TheraP cePSMA PET–positive cohort. We do not perform ^{18}F-FDG PET at treatment selection for ^{177}Lu-PSMA RLT, yet we strongly believe that our approach including contrast-enhanced CT within the PSMA ligand PET/CT reliably identifies PSMA-negative visceral lesions that are potentially ^{18}F-FDG PET–positive. Consequently, this type of disease does not constitute a further confounder in our data compared with TheraP. Our institutional approach is also supported by recent results from Seifert et al., who reported a substantial level of agreement in findings between PSMA ligand PET/CT and combined ^{18}F-FDG PET and PSMA ligand PET/CT for the assessment of therapy eligibility according to the VISION inclusion criteria (*16*). Although ^{18}F-FDG PET and PSMA PET provide complementary information, in only 5% of patients was incremental information derived from dual-tracer PET/CT imaging (*16*). However, in a recently published analysis by Buteau et al., an increased ^{18}F-FDG tumor volume (metabolic tumor volume ≥ 200 mL) in TheraP participants was significantly associated with lower rates of a maximum PSA decline of at least 50% (OR, 0.44; $P = 0.01$) and significantly correlated with a shorter PSA PFS (HR, 1.44; 95% CI, 1.28–2.52; $P = 0.03$) (*17*). Furthermore, in a retrospective analysis on patients who underwent ^{177}Lu-PSMA, the median OS was significantly shorter (6.0 mo) in patients with discordant ^{18}F-FDG–avid disease than in those without any ^{18}F-FDG–positive, PSMA-negative lesions (16.0 mo) (*18*). This finding further underpins the potential prognostic value of combined ^{18}F-FDG–negative, PSMA-negative PET imaging for treatment selection.

Sufficient PSMA ligand uptake of metastases in pretherapeutic PET is a prerequisite before PSMA RLT. However, no consensus on what should be considered sufficient exists (*19*). It is hypothesized that higher ^{68}Ga-PSMA-11 uptake correlates with higher absorbed doses of ^{177}Lu-PSMA, resulting in a favorable treatment response (*9*). Thus, it seems reasonable to restrict RLT to patients presenting with high ^{68}Ga-PSMA-11 tumor uptake to increase treatment response and avoid unnecessary side effects in patients unlikely to respond. In our exploratory analysis using different SUV_{max} thresholds between 10 and 50 for the hottest lesion, no clear trend on patient outcome as measured by PSA response (range, 52.8%–55.6%) or OS (range, 15.0–18.5 mo) in the cePSMA PET–positive group was observed (Supplemental Table 1). This observation is in line with results from Seifert et al., who demonstrated no significant correlation between the highest SUV_{max} in a single lesion and OS (*20*). Similarly, Ferdinandus et al. found no significant correlation between uptake in pretherapeutic PET (SUV_{max} of different types of metastases and different tumor-to-normal organ ratios) (*21*).

In the cePSMA PET–negative group, outcome measurements tend to be worse in the lower than higher SUV_{max} threshold groups. PSA response ranged from 17.2% to 38.3% and median OS from 9.5 to 12.0 mo using SUV_{max} thresholds from 10 to 50 (Supplemental Table 1). One possible explanation could be that at decreasing SUV_{max} thresholds for the hottest lesion, the cePSMA PET–negative group contains a higher rate of patients with lesions below an SUV_{max} of 10. For example, at SUV_{max} thresholds of 50, 35, and 10 for the hottest lesion, 14 of 60, 21 of 30, and 29 of 29 patients, respectively, were classified as cePSMA PET–negative based on measurable lesions with an SUV_{max} of below 10 (Supplemental Table 1). This demonstrates an increasing selection of patients with a generally lower lesion uptake in the cePSMA PET–negative group, potentially explaining the lower response. Thus, a hypothesis might be that insufficient PSMA ligand uptake in lesions in general might be more relevant for PSMA RLT outcome than a single

hottest lesion. This hypothesis is also supported by a substudy from Kuo et al. investigating the association between imaging parameters from baseline ^{68}Ga-PSMA-11 PET/CT scans in the ^{177}Lu-PSMA-617 arm of the VISION trial and clinical outcome (*22*). In this study, no significant correlation between SUV_{max} and treatment response or OS was found. However, a rising whole-body SUV_{mean} correlated with survival and treatment response, supporting our hypothesis that insufficient PSMA ligand uptake in lesions in general might play a crucial role for the outcome of PSMA RLT. This result is also in line with results from Gafita et al. demonstrating rising values of tumor SUV_{mean} to be significantly correlated with better outcome (*23*).

There are several limitations to our analysis, including its retrospective nature. In addition, although we could assess the impact of the TheraP criteria used in ^{68}Ga-PSMA-11 PET on treatment outcome, our cohort did not undergo additional ^{18}F-FDG PET. Thus, exact comparison with the TheraP cohort is not possible. Nevertheless, we believe that our approach including contrast-enhanced CT in the pretherapeutic workup selects most ^{18}F-FDG–positive, PSMA-negative disease, as discussed.

CONCLUSION

The results of our analysis demonstrate a better treatment response and outcome in mCRPC patients who underwent ^{177}Lu-PSMA RLT and retrospectively fulfilled the ^{68}Ga-PSMA-11–based TheraP inclusion criteria. However, as a relevant number of patients not fulfilling these stricter criteria also showed substantial rates of response, it remains to be discussed whether PSMA RLT needs to be withheld from these patients. Finally, our exploratory analyses using different SUV_{max} thresholds for the hottest lesion indicate that this criterion in TheraP is less prognostic than insufficient PSMA ligand uptake of lesions in general.

DISCLOSURE

Matthias Eiber reports fees from Blue Earth Diagnostics Ltd. (consultant, research funding), Novartis/AAA (consultant), Telix (consultant), Bayer (consultant, research funding), RayzeBio (consultant), Point Biopharma (consultant), Janssen Pharmaceuticals (consultant, speakers' bureau), Parexel (image review), and Bioclinica (image review) outside the submitted work and a patent application for rhPSMA. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is retrospective application of different TheraP PET-based inclusion criteria in mCRPC patients treated with RLT associated with higher rates of maximum PSA decline of at least 50%, and does it correlate with longer PSA PFS and OS?

PERTINENT FINDINGS: Retrospective application of the criteria was associated with higher rates of maximum PSA decline of at least 50% and significantly correlated with longer PSA PFS and OS.

IMPLICATIONS FOR PATIENT CARE: The ^{68}Ga-PSMA-11–based PET selection criteria used in TheraP are highly prognostic of better treatment outcome. The SUV_{max} threshold for the hottest lesions seems to be less relevant than insufficient PSMA ligand uptake in lesions in general.

REFERENCES

1. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med.* 2017;58:85–90.
2. Hofman MS, Violet J, Hicks RJ, et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* 2018;19:825–833.
3. Heck MM, Tauber R, Schwaiger S, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with ^{177}Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. *Eur Urol.* 2019;75:920–926.
4. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385:1091–1103.
5. Kratochwil C, Fendler WP, Eiber M, et al. EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging.* 2019;46:2536–2544.
6. Iravani A, Violet J, Azad A, Hofman MS. Lutetium-177 prostate-specific membrane antigen (PSMA) theranostics: practical nuances and intricacies. *Prostate Cancer Prostatic Dis.* 2020;23:38–52.
7. Hofman MS, Emmett L, Sandhu S, et al. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet.* 2021;397:797–804.
8. Karimzadeh A, Heck M, Tauber R, et al. ^{177}Lu-PSMA-I&T for treatment of metastatic castration-resistant prostate cancer: prognostic value of scintigraphic and clinical biomarkers. *J Nucl Med.* 2023;64:402–409.
9. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of ^{177}Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. *J Nucl Med.* 2019;60:517–523.
10. Weineisen M, Simecek J, Schottelius M, Schwaiger M, Wester HJ. Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer. *EJNMMI Res.* 2014;4:63.
11. Eder M, Neels O, Müller M, et al. Novel preclinical and radiopharmaceutical aspects of [^{68}Ga]Ga-PSMA-HBED-CC: a new PET tracer for imaging of prostate cancer. *Pharmaceuticals (Basel).* 2014;7:779–796.
12. Capobianco N, Sibille L, Chantadisai M, et al. Whole-body uptake classification and prostate cancer staging in ^{68}Ga-PSMA-11 PET/CT using dual-tracer learning. *Eur J Nucl Med Mol Imaging.* 2022;49:517–526.
13. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016;34:1402–1418.
14. Hofman MS, Emmet L, Sandhu S, et al. TheraP: [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—overall survival after median follow-up of 3 years (ANZUP 1603). *J Clin Oncol* [abstract]. 2022;40(suppl 16):5000.
15. Manafi-Farid R, Harsini S, Saidi B, et al. Factors predicting biochemical response and survival benefits following radioligand therapy with [^{177}Lu]Lu-PSMA in metastatic castrate-resistant prostate cancer: a review. *Eur J Nucl Med Mol Imaging.* 2021;48:4028–4041.
16. Seifert R, Telli T, Hadaschik B, Fendler WP, Kuo PH, Herrmann K. Is ^{18}F-FDG PET needed to assess ^{177}Lu-PSMA therapy eligibility? A VISION-like, single-center analysis. *J Nucl Med.* 2023;64:731–737.
17. Buteau JP, Martin AJ, Emmett L, et al. PSMA PET and FDP PET as predictors of response and prognosis in a randomized phase 2 trial of ^{177}Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic, castration-resistant prostate cancer (mCRPC) progressing after docetaxel (TheraP ANZUP 1603). *J Clin Oncol* [abstract]. 2022;40(suppl 6):10.
18. Michalski K, Ruf J, Goetz C, et al. Prognostic implication of dual tracer PET/CT: PSMA ligand and [^{18}F] FDG PET/CT in patients undergoing [^{177}Lu] PSMA radioligand therapy. *Eur J Nucl Med Mol Imaging.* 2021;48:2024–2030.
19. Kratochwil C, Fendler WP, Eiber M, et al. EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging.* 2019;46:2536–2544.
20. Seifert R, Seitzer K, Herrmann K, et al. Analysis of PSMA expression and outcome in patients with advanced prostate cancer receiving ^{177}Lu-PSMA-617 radioligand therapy. *Theranostics.* 2020;10:7812–7820.
21. Ferdinandus J, Eppard E, Gaertner FC, et al. Predictors of response to radioligand therapy of metastatic castrate-resistant prostate cancer with ^{177}Lu-PSMA-617. *J Nucl Med.* 2017;58:312–319.
22. Kuo PH, Hesterman J, Amstrong AJ, et al. [^{68}Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [^{177}Lu]Lu-PSMA-617 in patients with mCRPC. *J Clin Oncol* [abstract]. 2022;40(suppl 16):5002.
23. Gafita A, Calais J, Grogan TR, et al. Nomograms to predict outcomes after ^{177}Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. *Lancet Oncol.* 2021;22:1115–1125.