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Pretherapeutic PSMA PET-Derived Semiquantitative Parameters as Predictors of PSA Response in Patients with mCRPC Receiving [^{177}Lu]Lu-PSMA-617 Radioligand Therapy

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Abstract

Objective [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 radioligand therapy (RLT) shows promise for metastatic castration-resistant prostate cancer (mCRPC) patients with positive PSMA positron emission tomography (PET) imaging. Identifying high-risk patients is crucial. We evaluated pretherapeutic PSMA PET-derived parameters to predict prostate-specific antigen (PSA) response in patients undergoing [^{177}Lu]Lu-PSMA-617 RLT.

Materials and Methods We conducted a retrospective analysis among 27 patients (mean age: 71.0 ± 9.5 years; range: 52–85 years) who underwent PSMA PET/computed tomography (CT) and subsequent [^{177}Lu]Lu-PSMA-617 RLT between March 2019 and January 2023. After excluding patients with liver metastases, the number of patients left for analysis was 21 (14 responders and 7 nonresponders). Tumors were semiautomatically delineated with calculation of total tumor volume (PSMA-TV), lesion uptake (PSMA-TLU = PSMA-TV * standardized uptake value [SUV]mean), and lesion quotient (PSMA-TLQ = PSMA-TV/SUVmean) for each patient. Semiquantitative parameters were analyzed only in patients with mCRPC and no liver metastasis.

Results In total, 17/27 patients (62.96%) had a decline in PSA levels; 15/27 patients (55.56%) experienced a decline of > 50%. Pretherapeutic PSMA PET/CT results revealed significant differences in PSMA-TV ($p = 0.003$), PSMA-TLU ($p = 0.013$), and PSMA-TLQ ($p = 0.011$) between responders and nonresponders. SUVmax was significantly correlated to the best percentage change in PSA response after ^{177}Lu-PSMA-617 treatment

Keywords
- pretherapeutic PSMA PET
- metastatic castration-resistant prostate cancer
- liver metastasis
- [^{177}Lu]Lu-PSMA-617
- radioligand therapy

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($r = -0.79$, $p = 0.006$). No association was observed between PSMA-TV ($p = 0.367$), PSMA-TLU ($p = 0.128$), and PSMA-TLQ ($p = 0.556$), with the best percentage change in PSA response after ^{177}Lu-PSMA-617 therapy.

Conclusion Pretherapeutic PSMA PET-derived PSMA-TV, PSMA-TLU, and PSMA-TLQ were significant negative predictors of PSA response in patients with mCRPC and no liver metastasis receiving [^{177}Lu]Lu-PSMA-617 RLT.

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is a debilitating stage of prostate cancer with poor prognosis. Despite various therapeutic modalities to prolong disease progression and survival, this stage of cancer remains incurable.[1,2] The treatment of mCRPC has been revolutionized with the advent of [^{177}Lu]Lu-PSMA-617 (lutetium-177-labeled prostate-specific membrane antigen) radioligand therapy (RLT) for selectively delivering β-particle radiation to PSMA-positive cancer cells and their surrounding microenvironments.[3–5] Studies have demonstrated that [^{177}Lu]Lu-PSMA-617 therapy leads to a biochemical response, defined as a decline in prostate-specific antigen (PSA) levels by at least 50% from baseline in 45 to 66% of patients.[6–8] According to the VISION trial, the addition of [^{177}Lu]Lu-PSMA-617 RLT to standard care could prolong imaging-based progression-free survival (PFS) and overall survival (OS) in patients with advanced PSMA-positive mCRPC.[9] In several clinical studies, approximately 50% of enrolled participants had a PSA response with a decrease in PSA levels. However, 30% of patients experienced progressive disease, as evidenced by an increase in PSA levels greater than 25%.[10] The correlation between early changes in PSA levels after [^{177}Lu]Lu-PSMA-617 therapy, long-term biochemical response, and OS, as shown in PSMA positron emission tomography (PET) imaging, has been well established in the literature.[11,12]

Several predictive factors are identified for the response to [^{177}Lu]Lu-PSMA-617 therapy and OS. The detection of biomarkers associated with a response to treatment and overall outcome is crucial for early management and better patient outcomes. A well-established negative prognostic factor in prostate cancer is high disease volume. The establishment of reliable predictive markers can facilitate personalized treatment approaches and improve patient outcomes.[13,14] However, evidence regarding the prognostic value of total tumor volume (PSMA-TV) in patients treated with [^{177}Lu]Lu-PSMA-617 therapy is conflicting. In one study, no statistically significant correlation was found between PSMA-TV and OS in patients treated with Lu-PSMA.[11] Another preliminary analysis yielded a significant association of PSMA-TV with OS in patients treated with [^{177}Lu]Lu-PSMA-617.[15,16]

Assessment of PSMA-TV's prognostic significance is critical to determining its usefulness as a predictor of therapy intensification in patients receiving [^{177}Lu]Lu-PSMA-617 therapy. Several key prognostic parameters obtained from pretherapeutic PSMA PET imaging are the subject of ongoing debate, including the standardized uptake value (SUVmax and SUVmean), PSMA-TLU (total lesion uptake), and PSMA-TLQ (total lesion quotient). The accuracy and utility of these parameters as predictors of therapeutic response remain unresolved.[15] Hence, the objective of this study was to investigate the predictive value of PSMA PET-derived semiquantitative parameters for PSA response in patients with mCRPC receiving [^{177}Lu]Lu-PSMA-617 therapy.

Methods

Patients and Eligibility for [^{177}Lu]Lu-PSMA-617 Therapy

This retrospective study was performed in patients with mCRPC referred for [^{177}Lu]Lu-PSMA-617 therapy between March 2019 and January 2023. The inclusion criteria were patients with a diagnosis of mCRPC and disease progression following previous treatments, in line with androgen deprivation therapy (ADT) and second-line regimens such as abiraterone acetate, enzalutamide, or taxane-based chemotherapy, or those deemed unsuitable for chemotherapy owing to comorbidities or other medical conditions. The decision to administer [^{177}Lu]Lu-PSMA-617 therapy was made on a case-by-case basis by the interdisciplinary tumor board, which comprised experts from various medical disciplines, including oncologists, nuclear medicine physicians, and radiologists. Pretherapeutic PSMA PET findings guide the selection of patients for [177Lu]Lu-PSMA-617 therapy; both primary and all metastatic lesions must exhibit an uptake equal to or greater than the normal liver parenchymal uptake. The study assessed clinical outcomes, particularly the PSA response, and examined prognostic values associated with [177Lu]Lu-PSMA-617 therapy. It involved semiquantitative parameters obtained from pretherapeutic PSMA PET, encompassing SUVmax, SUVmean, PSMA-TV, PSMA-TLU, and PSMA-TLQ. Details regarding inclusion and exclusion patients are provided in ►**Supplementary Fig. S1** (available in the online version). This study was approved by the Human Research Ethics Committee (reference no.: 016/2565).

PSMA PET Imaging

We performed 18F-PSMA-1007 PET imaging using a 64-slice Siemens Biograph Vision scanner (Siemens Healthineers, Erlangen, Germany). All patients received an intravenous injection of 18F-PSMA-1007 at a dose of 2.59 MBq/kg over a period of approximately 60 minutes. In addition to the 18F-PSMA-1007 PET scan, a noncontrast-enhanced computed

tomography (CT) scan was performed for the purpose of attenuation correction. The parameters for CT scan included a voltage of 120 kV, an effective mAs of 25, and CARE Dose 4D with a quality reference of 70.

The three-dimensional list mode technique with continuous bed motion was applied for the 18F-PSMA-1007 PET scan, with patients in a head-first supine position. The scanning speed was set at 1.6 to 1.8 mm/s. The data acquired from the 18F-PSMA-1007 PET scan were reconstructed using the TrueX + time-of-flight (Ultra HD PET) algorithm with two iterations and five subsets. In addition to reconstruction, scatter and decay correction were conducted to ensure the accuracy of images.

PSMA PET Image Analysis

In this study, Syngo.via research software (V50B; Siemens Healthcare) was used for image analysis. The process of semiautomated PSMA PET lesion delineation was performed using the MM Oncology package. Lean body mass or body weight was not used for the semiautomated calculation. A specific threshold generated automatically by the software default, defined as (2 * aorta SUVmean) + (2 * aorta SUV standard deviation), was used for segmentation. Any metastases with a maximum SUV greater than the aorta-specific threshold were segmented. Lesions with PSMA uptake less than the aorta-specific threshold were added manually; these lesions must demonstrate suspicious anatomical findings on CT, thereby reducing the likelihood of nonspecific benign inclusions. In cases of bone/bone marrow lesions without any CT abnormality, those with PSMA uptake less than the aorta-specific threshold are less likely to be truly bone metastases. These lesions are usually very small foci that do not significantly affect the overall PSMA-avid tumor burden calculated by semiquantitative parameters. Any lesions smaller than 0.5 mL were discarded. The volume of each individual lesion was calculated by determining a lesion-specific threshold, defined as 40% of the maximum local SUV. The volume of a segmented lesion was denoted as the TV. The TV of all lesions was summed for the whole-body PSMA-TV of each patient. In analogy to the fluorodeoxyglucose (FDG) total lesion glycolysis, the TV of each lesion was multiplied by its mean SUV. The resulting products were summed for the whole-body PSMA-TLU of all patients. Finally, the TV was divided by the mean SUV to obtain the whole-body PSMA-TLQ.

Administration of [^{177}Lu]Lu-PSMA-617 Therapy

The PSMA-617 precursor was supplied by the Center of Molecular Research in Moscow, Russia. The [^{177}Lu] lutetium was procured from ITG Isotopes Technology (Garching, Germany). The synthesis of [^{177}Lu]Lu-PSMA-617 (Lu-PSMA) was performed as previously described. Lu-PSMA was administered at a median dose of 7.02 GBq (with an interquartile range [IQR] of 6.5–7.43 GBq) to patients until the occurrence of disease progression, severe adverse reactions, change in the therapy regime, or death. The administration of Lu-PSMA was carefully monitored and regulated to ensure the best possible patient outcomes.

Statistical Analysis

Semiquantitative parameters are described as median and IQR. The Mann–Whitney *U* test or Student's *t*-test was used for comparison of semiquantitative parameters, depending on data characterization. Fisher's exact test was applied to assess the significant difference between PSA response groups (responders and nonresponders) and categorical parameters. The patients who experienced a decrease in PSA levels after [177Lu]Lu-PSMA-617 will be categorized in the responder group, while patients whose PSA levels increased or remained unchanged after [177Lu]Lu-PSMA-617 will be categorized in the nonresponder group. Statistical significance was set at $p < 0.05$. Stata software version 11 (StataCorp LLC, College Station, Texas, United States) was used for all analyses. Spearman's correlation coefficient was used for differences between semiquantitative parameters of pretherapeutic PSMA PET, PSA level at baseline, and best percentage change in PSA response after [^{177}Lu]Lu-PSMA-617. Logistic regression with odds ratios was reported for univariate analysis between semiquantitative parameters and PSA response groups. All semiquantitative parameters were analyzed only in patients with mCRPC and no liver metastasis.

Results

Patient Characteristics

The study included 27 patients with mCRPC (17 responders and 10 nonresponders) and the mean age was 71.0 ± 9.5 years (range: 52–85 years). Before treatment, all patients underwent PSMA PET/CT imaging. The patients were divided according to their response to treatment, as shown in ►**Table 1**.

The mean Gleason score was 8.15 ± 0.90, indicating high-grade prostate cancer. Previous treatments for prostate cancer varied among patients; most of them had received medical ADT and previous chemotherapy. Denosumab and bisphosphonates were less commonly used.

At baseline, standard laboratory values did not differ significantly between responders and nonresponders, except for alanine aminotransferase (ALT; $p = 0.009$) and alkaline phosphatase (ALP; $p = 0.038$). For responders, mean ALT levels at baseline were 15 U/L (IQR: 12–20 U/L) compared with 29 U/L (IQR: 17–52 U/L) for nonresponders. Moreover, nonresponders had higher ALP levels (237 U/L) than responders (108 U/L), suggesting that higher ALP levels may be linked to a poorer response to Lu-PSMA therapy.

The data revealed that 18.52% (5/27) of patients with prostate cancer had liver metastasis. Furthermore, there was a significantly higher incidence of liver metastasis in nonresponders (40.00%, 4/10) compared with responders (5.88%, 1/17). It is important to note that semiquantitative parameters were not analyzed in patients with liver metastasis. The *p*-value for comparison of liver metastasis between the two groups was 0.047, indicating a significant difference. Moreover, the presence of prostate tumor may be related to a better response to Lu-PSMA therapy. Specifically, a higher percentage of responders had a prostate tumor when

Table 1 Patient characteristics

Variable	Total	Responders ($N = 17$)	Nonresponders ($N = 10$)	*p*-Value
Age (y, mean ± SD)	71.22 ± 9.52	73.47 ± 2.15	67.40 ± 3.10	0.111
Gleason score	8.15 ± 0.90	8.17 ± 0.31	8.14 ± 0.40	0.964
Previous treatments (%)				
Radical prostatectomy	33.33	25.00	33.33	1.000
Local radiation therapy	33.33	25.00	33.33	1.000
Medical ADT	88.89	63.64	100.00	0.094
Surgical ADT	22.22	25.00	11.11	0.603
Previous chemotherapy	83.33	50.00	100.00	0.019[a]
Denosumab	5.55	8.33	0.00	1.000
Bisphosphonate	16.67	0.00	33.33	0.063
Palliative radiotherapy	22.22	25.00	11.11	0.603
Standard laboratory values at baseline				
Hb (g/dL)	11.4 (10.3–12.6)	11.6 (10.9–12.7)	11.2 (10.2–12.2)	0.466
WBC ($\times 10^3$/μL)	6.56 (6.07–9.18)	6.35 (6.06–7.00)	9.12 (6.51–11.9)	0.097
Platelets ($\times 10^3$/μL)	252 (226–302)	260 (243–278)	239 (205–357)	0.651
AST (U/L)	30 (22–48)	26 (20–33)	48 (27–56)	0.070
ALT (U/L)	17 (12–27)	15 (12–20)	29 (17–52)	0.009[a]
ALP (U/L)	134 (95–237)	108 (85–140)	237 (149–406)	0.038[a]
PSA (ng/L)	62.71 (15.03–448.30)	36.27 (9.83–395.6)	110.8 (41.70–480.27)	0.248
Cr (mg/dL)	0.92 ± 0.18	0.95 ± 0.04	0.87 ± 0.07	0.268
GFR (mL/min)	81.89 ± 13.92	79.36 ± 3.51	85.56 ± 5.20	0.316
Tumor at prostate (%, *N*)	81.48 (22)	94.12 (16)	60.00 (6)	0.047[a]
Site of metastasis lesions (%, *N*)				
Osseous	100.00 (27)	100.00 (17)	100.00 (10)	
Regional lymph nodes	66.67 (18)	70.59 (12)	60.00 (6)	0.683
Distant lymph nodes	40.74 (11)	47.06 (8)	30.00 (3)	0.448
Hepatic	18.52 (5)	5.88 (1)	40.00 (4)	0.047[a]
Other				
• LungLung	18.52 (5)	23.53 (4)	10.00 (1)	0.621
• Peritoneal	3.70 (1)	0.00 (0)	10.00 (1)	0.370
• Adrenal	3.70 (1)	5.88 (1)	0.00 (0)	1.000
• Pleural	3.70 (1)	5.88 (1)	0.00 (0)	1.000
Lu-PSMA therapy				
Number of Lu-PSMA cycles (min–max)	2.52 ± 1.45 (1–6)	3.12 ± 0.36	1.50 ± 0.17	0.003[a]
Median cumulative activity IQR (min–max)	384.80 (278.27–689.67) (130–1,109.31)	602.00 (360.00–807.32) (180–1,109.31)	367.24 (202.5–381.72) (130–427.5)	

Abbreviations: ADT, androgen deprivation therapy; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; Cr, creatinine; GFR, glomerular filtration rate; Hb, hemoglobin; IQR, interquartile range; Lu-PSMA, lutetium-177-labeled prostate-specific membrane antigen; PSA, prostate-specific antigen; SD, standard deviation; WBC, white blood cells.
Note: ALP and PSA are presented as median with IQR; Cr and GFR are presented as mean ± SD.
[a]Significant at $p < 0.05$.

compared with nonresponders. The median number of cycles for Lu-PSMA therapy was 2.52 ± 1.45 cycles, with a median cumulative activity of 384.80 mCi (IQR: 278.27–689.67 mCi). Nonresponders received fewer cycles of therapy than responders, emphasizing the need to optimize the treatment regimen to improve response rates.

Biochemical Response (PSA Response)

Response to treatment was evaluated using the Prostate Cancer Clinical Trials Working Group criteria (PCWG2) (20) to assess the last recorded PSA levels. As per the PCWG2 criteria, a response was characterized as a reduction of $\geq$ 50% in PSA levels, which allowed for biochemical evaluation of RLT. Of the 27 patients, 17 (62.96%) exhibited a decline in PSA levels, among which 15 (55.56%) showed a reduction in PSA levels of $>$ 50%. The average number of cycles in the responder group was 3.12 ± 0.36 cycles. Waterfall plots of the best percentage change in PSA response after [^{177}Lu]Lu-PSMA-617 therapy are illustrated in ►**Fig. 1** and the actual PSA levels at baseline, PSA levels posttreatment, and the corresponding percentage change in PSA are displayed in ►**Table 2**.

Liver Metastasis

Note that 18.52% (5/27) of patients with prostate cancer had liver metastasis, with a significantly higher incidence in nonresponders (40.00%, 4/10) than responders (5.88%, 1/17). A comparison of liver metastasis between the two groups yielded a p-value of 0.047, indicating a significant difference. Remarkably, all 5 patients with liver metastasis exhibited uptake equal to or greater than the surrounding normal liver parenchyma. Importantly, we measured all liver lesions using SUV, but we did not use this information for the prognostic analysis. Conversely, a comparison of other distant metastases encompassing distant lymph nodes, lungs, peritoneal region, and bones between the two groups yielded a p-value exceeding 0.05, indicating a lack of significant difference.

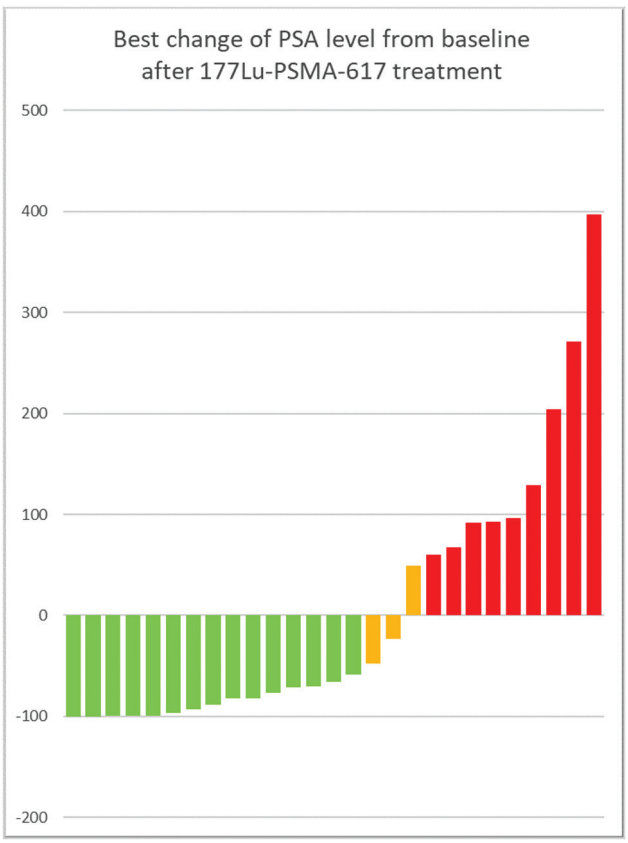

Fig. 1 Waterfall plots of best percentage change in prostate-specific antigen response after [^{177}Lu]Lu-PSMA-617 (lutetium-177-labeled prostate-specific membrane antigen) therapy.

Semiquantitative Parameters from Pretherapeutic PSMA PET

From the pretherapeutic PSMA PET/CT analysis, the median (IQR) SUVmax was 64.71 (41.96–86.66), that of whole-body SUVmean was 10.81 (7.74–12.99) and that of whole-body PSMA-TLU was 2,174.62 cm^3 (1,258.30–6,078.08). The average PSMA-TV and PSMA-TLQ were 314.91 ± 287.46 cm^3 and 29.08 ± 24.64, respectively. The semiquantitative parameters from pretherapeutic PSMA PET were stratified according to responders and nonresponders, as displayed in ►**Table 3**. PSMA-TV ($p = 0.003$), PSMA-TLU ($p = 0.013$), and PSMA-TLQ ($p = 0.011$) were significantly different between responders and nonresponders.

Finally, additional analysis revealed a statistically significant correlation between SUVmax and the best percentage change in the PSA response after [177Lu]Lu-PSMA-617 therapy ($r = -0.79$, $p = 0.006$). To calculate this percentage change, subtract the most lowered PSA level from the baseline PSA level and divide by the baseline PSA. However, PSMA-TV ($p = 0.367$), PSMA-TLU ($p = 0.128$), and PSMA-TLQ ($p = 0.556$) were not associated with the best percentage change in PSA response after [^{177}Lu]Lu-PSMA-617. The median time interval between pretherapeutic PSMA PET/CT and Lu-177 PSMA therapy was 22 days (IQR, 15–32.5 days). Furthermore, a multivariate analysis was not conducted due to the limited size of the population.

Discussion

In this study, we aimed to assess the utility of pretherapeutic PSMA PET as a potential biomarker for predicting the biochemical response (PSA response) of patients with mCRPC who were receiving Lu-PSMA therapy. Specifically, we evaluated semiquantitative parameters derived from PSMA PET imaging as a tool for prognostication. In accordance with the findings of a meta-analysis, strong evidence shows an association between visceral metastases and poor outcomes in [^{177}Lu]Lu-PSMA RLT, specifically in terms of biochemical response, PFS, and OS.[16] Our results also suggested that patients with liver metastases had a poorer biochemical response.[16] Non-PSMA avid mCRPC is not eligible for PSMA treatment. All metastatic lesions in this study exhibit sufficient PSMA expression, including liver metastases. However, as previously mentioned, liver metastases present challenges in delineating a proper region of interest due to the high physiologic hepatic background.

Table 2 Actual prostate-specific antigen (PSA) levels at baseline, PSA levels posttreatment, and the corresponding percentage change in PSA

	Patient number	Baseline PSA (ng/L)	PSA after treatment (ng/L)	PSA change (%)
Responders	1	29.900	0.013	–99.96
	2	0.451	0.001	–99.78
	3	84.500	0.259	–99.69
	4	544.560	2.120	–99.61
	5	395.600	1.660	–99.58
	6	62.710	0.732	–98.83
	7	87.200	3.380	–96.12
	8	5.720	0.420	–92.66
	9	501.000	88.780	–82.28
	10	1,587.000	285.000	–82.04
	11	9,866.000	2,289.000	–76.80
	12	75.300	21.800	–71.05
	13	9.870	2.920	–70.42
	14	28.820	9.960	–65.44
	15	3.040	1.260	–58.55
	16	36.270	18.840	–48.06
	17	9.830	7.580	–22.89
Nonresponders	18	126.900	189.300	49.17
	19	516.840	826.000	59.82
	20	37.470	62.600	67.07
	21	425.250	716.000	68.37
	22	1,893.440	3,628.660	91.64
	23	94.700	186.000	96.41
	24	5.510	12.600	128.68
	25	20.200	61.500	204.46
	26	54.400	202.000	271.32
	27	1,000.000	4,971.000	397.10

Previous studies have reported that early PSA changes following PSMA-RLT could predict the long-term biochemical and PET imaging response, as well as OS. PSA progression at 6 weeks often causes imaging-based progression within 12 weeks, necessitating treatment discontinuation. A 25% PSA increase at 6 weeks is associated with shorter OS. Monitoring early PSA changes can aid treatment decisions with control for imaging-based progression and survival

Table 3 Univariate analysis of semiquantitative parameters from pretherapeutic PSMA PET

Variable	Total	Responders	Nonresponders	Odds ratio	*p*-Value
SUVmax	64.71 (41.96–86.66)	53.41 (36.34–78.94)	81.95 (62.25–99.14)	–	0.187
SUVmean	10.81 (7.74–12.99)	9.40 (7.16–11.95)	13.02 (12.46–13.47)	–	0.058
PSMA-TV	314.91 ± 287.46	199.00 ± 35.51	585.37 ± 154.22	0.993	0.033[a]
PSMA-TLU	2,174.62 (1,258.30–6,078.08)	1,891.19 (679.23–3,582.68)	7,000.76 (3,595.76–8,861.65)	0.999	0.039[a]
PSMA-TLQ	29.08 ± 24.64	20.38 ± 3.77	49.38 ± 13.43	0.944	0.040[a]

Abbreviations: PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SUV, standardized uptake value; TLQ, total lesion quotient; TLU, total lesion uptake; TV, total tumor volume.
Note: SUVmax, SUVmean, and PSMA-TLU are presented as median (interquartile range); PSMA-TV and PSMA-TLQ are presented as mean ± standard deviation.
[a]Signifies statistical significance.

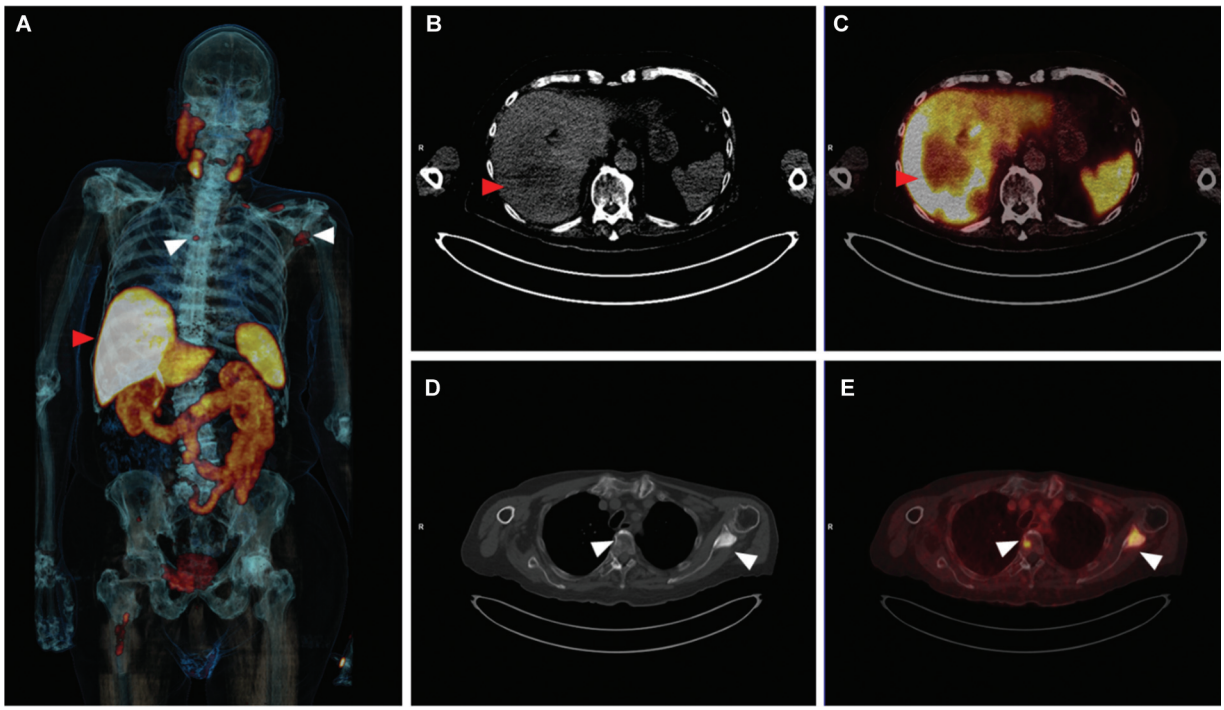

Fig. 2 An 84-year-old man with metastatic castration-resistant prostate cancer underwent pretherapeutic ^{18}F-prostate-specific membrane antigen (PSMA)-1007 positron emission tomography/computed tomography (PET/CT) imaging before receiving [^{177}Lu]Lu-PSMA-617 treatment. (**A**) Maximum intensity projection image of the ^{18}F-PSMA-1007 PET/CT; (**B**) axial CT image revealing multiple hypodense lesions in the liver; (**C**) corresponding fused axial ^{18}F-PSMA-1007 PET/CT image showing heterogeneous prostate-specific membrane antigen (PSMA) uptake in these hepatic lesions, as well as high physiologic uptake in the liver parenchyma; (**D**, **E**) axial CT image and corresponding fused axial ^{18}F-PSMA-1007 PET/CT image revealing osteoblastic bone lesions at the thoracic vertebra and left scapula, likely PSMA-avid bone metastases.

outcomes.[11,12] Furthermore, a recent meta-analysis demonstrated that PSMA-Radio-Ligand-Therapy (PRLT) leads to a higher proportion of patients exhibiting a positive response to treatment, with a decline in PSA of $\geq$ 50%, compared with control groups. Additionally, a decline in PSA and PSA decline of $\geq$ 50% could be associated with prolonged survival after RLT.[17] In a large, real-world cohort of patients with late-stage or end-stage mCRPC treated with [^{177}Lu]Lu-PSMA RLT, the best PSA response rate, defined as a reduction of $\geq$ 50% in PSA levels, was observed in 52.0% of patients.[18] Our study, which included 27 patients, showed that 62.96% of patients experienced a PSA decline and 55.56% had a decline greater than 50%, qualifying them as responders.

The presence of visceral metastases was associated with poor response and survival outcomes in patients with mCRPC treated with Lu-PSMA RLT.[16] Those with liver metastases had worse OS duration than patients with lung metastases.[19,20] Additionally, the difficulties in accurate semiquantitative analysis of PSMA-avid liver metastasis owing to challenges in drawing a proper region of interest and high physiologic hepatic background, excluding liver metastasis, may provide more reliable and consistent results. This is because the presence of liver metastasis could be associated with a worse OS duration in patients with mCRPC, and may therefore confound analysis of the treatment response to Lu-PSMA therapy. Furthermore, previous studies have shown that the presence of visceral metastases, including liver metastasis, is associated with poorer response and survival outcomes in patients with mCRPC treated with Lu-PSMA RLT. By excluding patients with liver metastasis from the analysis, the efficacy of Lu-PSMA therapy could be better evaluated in those with mCRPC without the confounding factor of liver metastasis, as shown in ►**Fig. 2**.

However, a compelling study by Khreish et al revealed that [^{177}Lu]Lu-PSMA RLT resulted in a noteworthy biochemical response in 57% of patients with liver metastases, and the therapeutic response was independent of the hepatic tumor burden. These findings suggest that [^{177}Lu]Lu-PSMA RLT may be an encouraging approach for managing mCRPC with liver metastases. Nonetheless, it is crucial to acknowledge that in this study, only patients with intense PSMA uptake in liver lesion(s) $\geq$ 1.5 times the physiological liver uptake were recruited.[21]

Some hypotheses propose that visceral metastases could lead to reduced or lost PSMA expression and poor treatment outcomes owing to epigenetic alterations, including neuroendocrine transdifferentiation.[22,23] However, poor clinical outcomes are likely to result from various biological factors, including intrinsic tumor cell factors, tumor microenvironment, and systemic factors. Immunohistochemical studies have revealed increased expression of antiapoptotic nuclear surviving panel of survival proteins in visceral metastases.[24] However, liver metastases could exhibit a significant relative overexpression of proangiogenic factor angiopoietin-2.[25] On a systemic level, serum cytokine levels have been linked to the prognosis and presence of liver metastases in various

tumor types, despite no conclusive evidence of a correlation between circulating cytokines and visceral or liver metastases.

Taken together, these findings reveal that multiple factors contribute to poor clinical outcomes in patients with mCRPC. Furthermore, the presence of visceral or liver metastases is likely to be one of many important factors. Analyzing PSMA-avid liver metastases using semiquantitative parameters can be challenging owing to difficulties in drawing the region of interest and high levels of background activity in the liver. The presence of liver metastasis in patients with mCRPC has been associated with worse OS. This may confound analysis of the treatment response to Lu-PSMA therapy. Therefore, in patients with mCRPC and no liver metastases, semiquantitative parameters of pretherapeutic PSMA PET scans should be analyzed to evaluate the treatment response.

Debate on the use of PSMA PET-derived tumor volume as a predictor in prostate cancer is ongoing. Several studies have investigated the relationship between tumor volume and patient outcomes. For instance, Seifert et al reported that tumor volume was a negative predictor of OS,[15,26,27] and Ferdinandus et al showed that PSMA PET-derived tumor volume was statistically nonsignificant as a prognosticator.[28] In line with the concept of theranostics, higher SUVmean is related to higher tumor doses in Lu-PSMA therapy, and may therefore be linked to a favorable outcome.[4]

Notably, high PSMA expression can also serve as a marker for aggressive tumor phenotypes. In particular, during the primary staging of prostate cancer, strong PSMA expression is correlated with higher Gleason scores.[29] Integrating tumor volume and SUV to form a combined biomarker appears reasonable in the context of FDG total lesion glycolysis. However, because tumor volume is a negative predictor and SUV uptake is a positive predictor, these parameters may counteract each other in the PSMA-TLU biomarker.

Seifert et al proposed PSMA-TLQ as the quotient of total tumor volume and SUVmean. According to their findings, PSMA-TLQ might serve as a more effective prognosticator of survival compared with lesion number and even PSMA-TV. Furthermore, PSMA-TLQ maintained its status as an independent prognosticator of survival in a multivariate regression analysis involving PSA blood levels.[27] Our data also supported the significance of PSMA-TLQ, indicating a significant difference between responders and nonresponders, consistent with the earlier study. However, our research revealed that PSMA-TV and PSMA-TLU were also significantly different between responders and nonresponders, suggesting that these parameters could potentially serve as negative prognosticators of PSA response.

The underlying reasons for favorable outcomes in patients with mCRPC and strong PSMA expression are yet to be fully understood, owing to uncertainty regarding higher dose delivery, lesser dedifferentiation, or a combination of both. The use of SUVmax as a prognosticator remains a controversial topic. Widjaja et al demonstrated a correlation between pretherapeutic SUVmax and PSA change after two cycles, but none for PSMA-TV and whole-body total lesion PSMA.[30]

In a separate investigation, ALP was a significant, independent factor that could predict changes in PSA levels among patients with bone metastases who underwent [^{177}Lu]Lu-PSMA RLT.[31] Of note, in our investigation, we found that these parameters exhibited statistical significance in the initial analysis.

The present analysis has some limitations. First, the analysis was conducted retrospectively, which may introduce selection bias. Furthermore, tumor volume was determined as a whole-body metric rather than on an organ-specific basis. Additionally, owing to factors such as being a single-center study, high-cost treatment, and limited accessibility, the sample size was limited, which could impact generalizability of the results. However, this was the first study to perform semiquantitative analysis in patients with mCRPC without liver metastasis. Our findings will provide valuable evidence to support the use of [^{177}Lu]Lu-PSMA-617 RLT and assist in prognostic evaluation of these patients. Our results may also help to clarify actual significant prognostic factors. Despite these limitations, the potential impact of this study needs to be recognized. To further validate these findings, larger studies are needed to better understand the relationship between pretherapeutic PSMA PET measurements and treatment outcomes and to provide stronger evidence-based data on the use of PSMA PET measurements in clinical decision-making.

Conclusion

Pretherapeutic PSMA PET measurements, including PSMA-TV, PSMA-TLU, and PSMA-TLQ, were significant negative predictors of PSA response in patients with mCRPC without liver metastasis receiving Lu-PSMA therapy. Our findings suggest the potential use of pretherapeutic PSMA PET measurements as a tool for prognostic evaluation and patient selection for [177Lu]Lu-PSMA RLT. However, it is important to recognize that this trend in responsiveness remains preliminary, and an optimal cutoff value for patient selection before initiating treatment remains undefined. The imperative for more extensive investigations is underscored, as larger-scale studies are necessary to provide robust, evidence-based data concerning the integration of PSMA PET measurements into clinical decision-making.

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Conflict of Interest
None declared.

References

1 Sartor O, de Bono JS. Metastatic prostate cancer. N Engl J Med 2018;378(07):645–657
2 Nuhn P, De Bono JS, Fizazi K, et al. Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. Eur Urol 2019;75 (01):88–99

3 Afshar-Oromieh A, Hetzheim H, Kratochwil C, et al. The theranostic PSMA ligand PSMA-617 in the diagnosis of prostate cancer by PET/CT: biodistribution in humans, radiation dosimetry, and first evaluation of tumor lesions. J Nucl Med 2015;56(11): 1697–1705
4 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(04): 517–523
5 Banerjee S, Pillai MRA, Knapp FFR. Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications. Chem Rev 2015;115(08):2934–2974
6 Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med 2017;58(01):85–90
7 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(06):825–833
8 Hofman MS, Emmett L, Violet J, et al; ANZUP TheraP team. TheraP: a randomized phase 2 trial of ^{177}Lu-PSMA-617 theranostic treatment vs cabazitaxel in progressive metastatic castration-resistant prostate cancer (Clinical Trial Protocol ANZUP 1603). BJU Int 2019;124(Suppl 1):5–13
9 Sartor O, de Bono J, Chi KN, et al; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021;385(12):1091–1103
10 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 (12):4028–4041
11 Gafita A, Heck MM, Rauscher I, et al. Early prostate-specific antigen changes and clinical outcome after ^{177}Lu-PSMA radionuclide treatment in patients with metastatic castration-resistant prostate cancer. J Nucl Med 2020;61(10):1476–1483
12 Kind F, Fassbender TF, Andrieux G, Boerries M, Meyer PT, Ruf J. Early PSA change after [^{177}Lu]PSMA-617 radioligand therapy as a predicator of biochemical response and overall survival. Cancers (Basel) 2021;14(01):149
13 Kyriakopoulos CE, Chen Y-H, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36(11):1080–1087
14 Sweeney CJ, Chen Y-H, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373(08):737–746
15 Mokoala K, Lawal I, Lengana T, et al. PSMA theranostics: science and practice. Cancers (Basel) 2021;13(15):3904
16 Satapathy S, Mittal BR, Sood A. Visceral metastases as predictors of response and survival outcomes in patients of castration-resistant prostate cancer treated with 177Lu-labeled prostate-specific membrane antigen radioligand therapy: a systematic review and meta-analysis. Clin Nucl Med 2020;45(12):935–942
17 Sadaghiani MS, Sheikhbahaei S, Werner RA, et al. ^{177}Lu-PSMA radioligand therapy effectiveness in metastatic castration-resistant prostate cancer: An updated systematic review and meta-analysis. Prostate 2022;82(07):826–835
18 Khreish F, Ghazal Z, Marlowe RJ, et al. 177 Lu-PSMA-617 radioligand therapy of metastatic castration-resistant prostate cancer: Initial 254-patient results from a prospective registry (REALITY Study). Eur J Nucl Med Mol Imaging 2022;49(03):1075–1085
19 Ahmadzadehfar H, Rahbar K, Baum RP, et al. Prior therapies as prognostic factors of overall survival in metastatic castration-resistant prostate cancer patients treated with [^{177}Lu]Lu-PSMA-617. A WARMTH multicenter study (the 617 trial). Eur J Nucl Med Mol Imaging 2021;48(01):113–122
20 Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol 2016;34(14): 1652–1659
21 Khreish F, Kochems N, Rosar F, et al. Response and outcome of liver metastases in patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing ^{177}Lu-PSMA-617 radioligand therapy. Eur J Nucl Med Mol Imaging 2021;48(01):103–112
22 Pouessel D, Gallet B, Bibeau F, et al. Liver metastases in prostate carcinoma: clinical characteristics and outcome. BJU Int 2007;99 (04):807–811
23 Parimi V, Goyal R, Poropatich K, Yang XJ. Neuroendocrine differentiation of prostate cancer: a review. Am J Clin Exp Urol 2014;2 (04):273–285
24 Akfirat C, Zhang X, Ventura A, et al. Tumour cell survival mechanisms in lethal metastatic prostate cancer differ between bone and soft tissue metastases. J Pathol 2013;230(03):291–297
25 Morrissey C, True LD, Roudier MP, et al. Differential expression of angiogenesis associated genes in prostate cancer bone, liver and lymph node metastases. Clin Exp Metastasis 2008;25(04): 377–388
26 Seifert R, Herrmann K, Kleesiek J, et al. Semiautomatically quantified tumor volume using ^{68}Ga-PSMA-11 PET as a biomarker for survival in patients with advanced prostate cancer. J Nucl Med 2020;61(12):1786–1792
27 Seifert R, Kessel K, Schlack K, et al. PSMA PET total tumor volume predicts outcome of patients with advanced prostate cancer receiving [^{177}Lu]Lu-PSMA-617 radioligand therapy in a bicentric analysis. Eur J Nucl Med Mol Imaging 2021;48(04):1200–1210
28 Ferdinandus J, Violet J, Sandhu S, et al. Prognostic biomarkers in men with metastatic castration-resistant prostate cancer receiving [177Lu]-PSMA-617. Eur J Nucl Med Mol Imaging 2020;47(10): 2322–2327
29 Uprimny C, Kroiss AS, Decristoforo C, et al. ^{68}Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. Eur J Nucl Med Mol Imaging 2017;44(06):941–949
30 Widjaja L, Werner RA, Ross TL, Bengel FM, Derlin T. PSMA expression predicts early biochemical response in patients with metastatic castration-resistant prostate cancer under ^{177}Lu-PSMA-617 radioligand therapy. Cancers (Basel) 2021;13(12): 2938
31 Derlin T, Sommerlath Sohns JM, Schmuck S, et al. Influence of short-term dexamethasone on the efficacy of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. Prostate 2020;80(08):619–631

