^{177}Lu-PSMA-I&T for Treatment of Metastatic Castration-Resistant Prostate Cancer: Prognostic Value of Scintigraphic and Clinical Biomarkers

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The aim of this retrospective analysis was to determine prostate-specific antigen (PSA) response, PSA progression-free survival (PFS), and overall survival (OS) in a large cohort of patients with metastatic castration-resistant prostate cancer (mCRPC) treated with ^{177}Lu-PSMA-I&T and to identify clinical and scintigraphic prognostic factors for outcome. **Methods:** In total, 301 consecutive mCRPC patients were included in this analysis. Prognostic factors included clinical parameters, routine laboratory parameters, and findings on posttreatment scintigraphy. Scintigraphic tumor uptake of ^{177}Lu-PSMA-I&T was compared with salivary gland uptake and classified as high or low. The longest extent of skeletal metastatic disease was measured, and its changes during therapy were used to define scintigraphic progression, response, and stable disease. A PSA response of at least 50%, PSA PFS, and OS were calculated. **Results:** In total, 1,138 cycles (median, 3 cycles per patient) of ^{177}Lu-PSMA-I&T using a standard activity of 7.4 GBq were applied intravenously every 4–10 wk (median, 6 wk). Overall, 34% (95% CI, 28%–38%) of patients showed a PSA response of at least 50%, and the median PSA PFS and OS of the total patient cohort were 16.0 wk (95% CI, 12.1–19.9) and 13.8 mo (95% CI, 12.4–15.5), respectively. Patients with high scintigraphic tumor uptake showed a higher PSA response rate of at least 50% (45.7% vs. 10.4%; $P < 0.0001$) and a significantly reduced risk of PSA progression (median event time, 24.9 vs. 9.0 wk; hazard ratio, 0.3; 95% CI, 0.2–0.5; $P < 0.0001$). In our data, risk of death was not significantly different between patients with high scintigraphic uptake and those with low scintigraphic uptake (median, 14.4 vs. 12.4 mo; hazard ratio, 0.9; 95% CI, 0.6–1.3; $P = 0.6$). In a multivariable analysis, the following pretherapeutic prognostic factors for OS were identified: alkaline phosphatase, lactate dehydrogenase, and PSA levels; prior chemotherapy; and the presence of visceral metastases. Scintigraphic response was a strong prognostic factor for PSA response, PSA PFS, and OS after 1 treatment cycle. **Conclusion:** This retrospective analysis of a large group of consecutive patients corroborates previous clinical experience for ^{177}Lu-PSMA-I&T in mCRPC and establishes previously proposed prognostic factors. The skeletal tumor extent and its changes were identified as new potential biomarkers to predict the outcome of therapy after the first treatment cycle.

Key Words: ^{177}Lu-PSMA-I&T; metastatic castration-resistant prostate cancer (mCRPC); prognostic factors; scintigraphic biomarkers; clinical biomarkers

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Prostate-specific membrane antigen (PSMA)–targeted radioligand therapy (RLT) has increasingly emerged for therapy of patients with metastatic castration-resistant prostate cancer (mCRPC) who exhausted approved treatment regimens (*1,2*). For the PSMA ligand ^{177}Lu-PSMA-617, efficacy and low toxicity have been shown in several retrospective analyses and in 2 phase II prospective trials (*1,3,4*). Recently, prolonged overall survival (OS) and progression-free survival (PFS) were proven in a randomized phase III clinical trial just recently resulting in Food and Drug Administration approval (*5*). Further, clinical parameters such as prior chemotherapy, the presence of visceral metastases, and increased levels of serum lactate dehydrogenase (LDH) have been found to be negatively correlated with patient outcome (*6*).

Another PSMA ligand that has shown promise for therapy of mCRCP is ^{177}Lu-PSMA-I&T, although clinical experience is more limited (*7*). ^{177}Lu-PSMA-I&T is currently being explored in a multicenter, randomized prospective phase III trial in mCRPC prior chemotherapy (SPLASH, NCT04647526) after second-line hormonal treatment, with the first results expected in 2023.

Previously, results on 100 patients who underwent ^{177}Lu-PSMA-I&T RLT showed mild toxicity and good antitumor activity in late-stage mCRPC (*2*). A prostate-specific antigen (PSA) decline of at least 50% within 12 wk was associated with longer clinical PFS and OS. A subgroup analysis identified an association of visceral metastasis at baseline and increased LDH with worse outcome.

The first preliminary retrospective analyses indicate that intensity on posttherapeutic ^{177}Lu-PSMA scintigraphy could be predictive for PSA response, suggesting it as a simple, fast, and widely available imaging biomarker for therapy response (*8*). However, data are sparse, and impact on OS has not been evaluated. Our clinical experience indicates that the extent of disease and, specifically, infiltration of the appendicular skeleton on posttherapeutic scans and its change during ^{177}Lu-PSMA RLT also hold promise to serve as a new and potentially prognostic imaging biomarker.

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Thus, the aim of our retrospective analysis was to update our clinical experience with ^{177}Lu-PSMA-I&T; to evaluate, especially, the prognostic value of clinical and laboratory parameters; and to investigate the use of posttreatment whole-body scintigraphy to predict patient outcome.

MATERIALS AND METHODS

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

This retrospective analysis included 301 consecutive mCRPC patients receiving at least 2 cycles of ^{177}Lu-PSMA-I&T between December 2014 and July 2020. All patients had previously received second-line hormonal therapy with abiraterone or enzalutamide and chemotherapy or were unfit for chemotherapy. Patient characteristics are shown in Table 1. Before treatment, sufficient PSMA expression was confirmed by PSMA ligand PET imaging (^{68}Ga-PSMA-11, ^{18}F-PSMA-1007, ^{18}F-rhPSMA-7, or ^{18}F-rhPSMA-7.3). Only patients with PSMA ligand uptake in tumor lesions at least as high as liver background uptake were treated.

TABLE 1
Baseline Patient Characteristics

Characteristic	Data
No. of patients	301
Age (y), *n* = 301	73 (67–77)
PSA (ng/mL), *n* = 297	99.5 (20.4–290.3)
LDH (U/L), *n* = 297	263.5 (218–344)
AP (U/L), *n* = 297	112 (72–231)
Hemoglobin (g/dL), *n* = 297	11.7 (10.3–12.8)
Prior systemic therapies for mCRPC, *n* = 301	
Docetaxel	213
Cabazitaxel	48
Abiraterone	252
Enzalutamide	183
^{223}Ra	41
Previous chemotherapy	214
No. of prior mCRPC therapies, *n* = 301	
1	105
2	109
3	68
4	18
5	4
Site of metastasis, *n* = 301	
Lymph node, overall	216
Lymph node only (N1+/M1a)	22
Bone overall	274
Bone (M1b, without visceral metastases)	215
Visceral, overall (M1c)	64
Liver	26
Lung	31
Adrenal	21

Qualitative data are number and percentage; continuous data are median and interquartile range.

This patient population includes the 100 patients reported by Heck et al. but adds new patients and extended follow-up for the first 100 patients (*2*).

^{177}Lu-PSMA-I&T was prepared according to good manufacturing practice and the German Medicinal Products Act (arzneimittelgesetz §13 2b). The institutional ethics committee approved this retrospective analysis under reference number 115/18S, and all subjects gave written informed consent. Patients were treated under the conditions of the Declaration of Helsinki, article 37, "Unproven Interventions in Clinical Practice."

Whole-Body Scintigraphy and Image Analysis

Posttherapeutic whole-body scintigraphy (planar anterior and posterior views) was performed approximately 24 h after injection at every cycle using a Symbia T series camera (Siemens) with a medium-energy parallel-hole collimator, a scan speed of 20 cm/min, and 113 keV ± 20% and 208 keV ± 12% photopeak windows. All images were evaluated by one nuclear medicine physician in training under the supervision of one board-certified nuclear medicine physician with more than 7 y of experience in PSMA-targeted imaging and therapy.

The whole-body scans were analyzed for scintigraphic tumor uptake and the extent of skeletal metastatic disease. Tumor uptake of ^{177}Lu-PSMA-I&T on the first posttreatment scan was visually classified as high when most metastatic lesions exceeded the physiologic uptake of the salivary glands. If most lesions equaled or were lower than uptake in the salivary glands, the tumor uptake was classified as low. The extent of skeletal metastatic disease was assessed by a simple quantitative index, as follows. On the first posttherapy scintigram, the longest extent of metastatic disease in a single bone (e.g., femur) contributing to the appendicular skeleton (including clavicle, scapula, humerus, radius, ulna, and the pelvic bones, except the sacrum, femur, tibia, and fibula) was identified and its absolute extent was measured with a ruler. If metastatic bone infiltration was discontinuous in a particular bone, the extents of each site of metastatic disease were measured and summed. On the second posttherapy scintigram, the extent of the same metastatic site was reassessed. The absolute change between the first and second posttherapeutic scans was calculated and defined as change in infiltration length. Scintigraphic progression, response, and stable disease were defined as more than a 0.5-cm increase, more than a 0.5-cm decrease, and a ±0.5-cm change in infiltration length between the first and second cycles, respectively.

Clinical Parameters, PSA Response, and PSA Progression

The following pretherapeutic parameters were collected: age, alkaline phosphatase (AP), LDH, hemoglobin, and PSA, as well as their relative changes between the first and second cycles. PSA response was defined as a PSA decline of at least 50% from baseline according to the criteria of Prostate Cancer Clinical Trials Working group 3 (*9*). PSA progression was defined either as 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 (*9*).

Prior systemic therapies (including abiraterone, enzalutamide, first- and second-line chemotherapy, and ^{223}Ra) and metastatic patterns (N+/M1a, lymph node only disease; M1b, presence of bone metastases without visceral metastases; and M1c, presence of visceral metastases) derived from PSMA PET imaging were collected.

Statistical Analysis

Primary outcome measures were PSA response, OS, and PSA PFS. The Kaplan–Meier method was used to estimate event time distributions, and log-rank tests were used for group comparisons. To correct for log-rank test α-error accumulation, significance was assumed when *P* values were less than 0.016 (Bonferroni adjustment for impact

of infiltration length on OS and PSA PFS). Frequencies of PSA response were compared between groups using χ^2 tests.

Univariable and multivariable Cox regression analyses were performed to determine the association of pretherapeutic parameters, relative changes in laboratory parameters, and information from posttherapeutic scintigraphy (scintigraphic tumor uptake and change in infiltration length) with PSA PFS and OS. A subgroup analysis in patients without visceral metastases was performed given the known strong negative association of visceral metastases with outcome. The corresponding hazard ratios (HRs) and 95% CIs are presented. A P value of less than 0.05 was considered statistically significant.

For tumor uptake, as well as classification of scintigraphic response, stable disease, and progression, the Cohen κ-coefficient was calculated for intrarater reliability. Strength of agreement for κ values was interpreted according to the Landis and Koch benchmark scale (*10*).

χ^2 tests, Kaplan–Meier estimation, log-rank tests, and calculation of the Cohen κ-coefficient were performed using Prism (version 8.4.3; GraphPad Software) for Mac (Apple). Uni- and multivariable Cox regression analysis was performed using SPSS Statistics (version 25.0; IBM Corp.) for Windows (Microsoft).

RESULTS

In total, 301 patients were analyzed, and 1,138 cycles of PSMA RLT with a median of 3 cycles per patient (range, 2–20) were applied. The 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. The median time on treatment was 3 mo. Posttherapeutic scintigraphy and complete laboratory results were not available for 2 and 4 patients, respectively. At baseline, pelvic lymph nodes, extrapelvic lymph nodes, bone metastases, and visceral metastases were present in 159 (52.8%), 192 (63.8%), 274 (91.0%), and 64 (21.3%) patients, respectively. The median follow-up was 9 mo (range, 1–63 mo). One hundred one (34%; 95% CI, 28%–38%) patients achieved a PSA response after PSMA-targeted RLT. In the total patient cohort, median OS was 13.8 mo (95% CI, 12.4–15.5 mo) and median PSA PFS was 16.0 wk (95% CI, 12.1–19.9 wk). At the time of analysis, 226 patients had shown PSA progression and 182 patients had died.

Impact of Scintigraphic Tumor Uptake on PSA Response, PSA PFS, and OS

High (>salivary gland level) and low (≤salivary gland level) scintigraphic tumor uptake was observed in 202 (67.6%) and 97 (32.4%) patients, respectively. The classification as high or low uptake achieved substantial agreement for intrarater reliability (κ = 0.796). PSA response was achieved in 91 (45.7%) patients with high uptake versus 10 (10.4%) patients with low uptake ($P < 0.0001$; Fig. 1). Examples of patients with high and low uptake are presented in Figure 2.

PSA PFS in patients with high uptake was significantly longer than in those with low uptake (median, 24.9 vs. 9.0 wk; HR, 0.3; 95% CI, 0.2–0.5; $P < 0.0001$; Fig. 3A). OS did not significantly differ between patients with high uptake and those with low uptake (median, 14.4 vs. 12.4 mo; HR, 0.9; 95% CI, 0.6–1.3; $P = 0.6$; Fig. 3B). In the subgroup of patients without visceral metastases, higher rates of PSA response (50.3% vs. 12.5%) were achieved, and PSA PFS and OS were significantly longer in patients with high uptake (median, 26.7 vs. 9.0 wk; HR, 0.3; 95% CI, 0.2–0.4; $P < 0.0001$) than in those with low uptake (15.5 vs. 11.4 mo; HR, 0.6; 95% CI, 0.4–1.0; $P = 0.03$) (Figs. 3C and 3D).

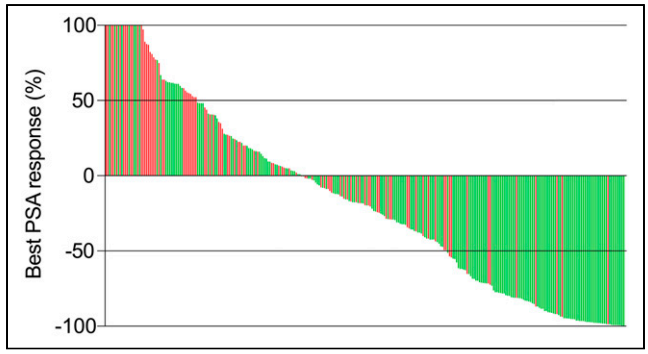

FIGURE 1. Waterfall plot showing response to treatment as measured by serum PSA. Best PSA response is defined as smallest increase or greatest decrease in PSA from baseline compared with color-coded ^{177}Lu-PSMA ligand uptake in posttherapeutic whole-body scintigraphy. First 21 columns represent patients with increase of >100% as best PSA response. Red = patients with low scintigraphic uptake on posttherapeutic scintigraphy; green = patients with high scintigraphic uptake on posttherapeutic scintigraphy.

Impact of Infiltration Length on PSA Response, PSA PFS, and OS

The median extent of metastases on the first and second posttreatment scans was 9.8 cm (range, 1.2–76.9 cm) and 10.3 cm (range, 0.0–78.4 cm), respectively. In 4 patients, the extents of metastatic disease in the femur and the tibia/fibula were summed because of a lack of delimitation of the infiltration path. No significant correlation between quartiles of the extent of disease and PSA PFS ($P = 0.4$) or OS ($P = 0.2$) was observed (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org).

Overall, 46 (24.7%), 65 (34.9%), and 75 (40.3%) patients showed scintigraphic response, stable disease, and progression, respectively. The classification of scintigraphic response, stable disease, and progression achieved substantial agreement for intrarater reliability (weighted κ = 0.711). A PSA response was achieved in 64.4%

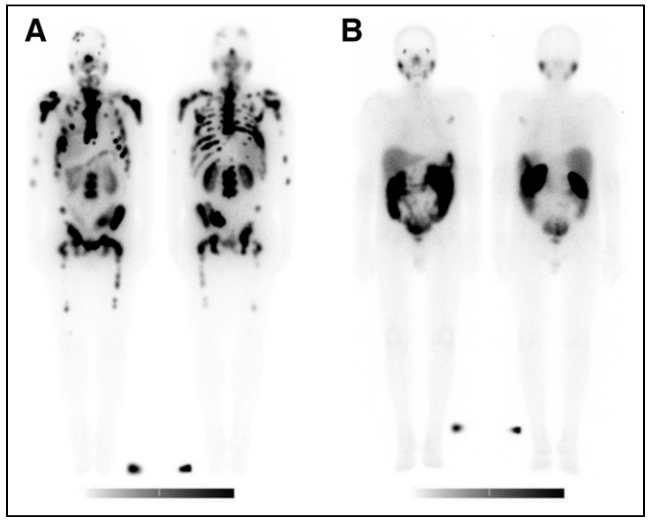

FIGURE 2. A 69-y-old patient with bone metastases presenting with high scintigraphic uptake (A) and a 76-y-old patient with bone and lymph node metastases presenting with low scintigraphic uptake (B) on posttherapeutic whole-body scintigraphy at first cycle of ^{177}Lu-PSMA-I&T. PSA PFS and OS were 58 wk and 24 mo, respectively, in patient A and 17 wk and 10 mo, respectively, in patient B.

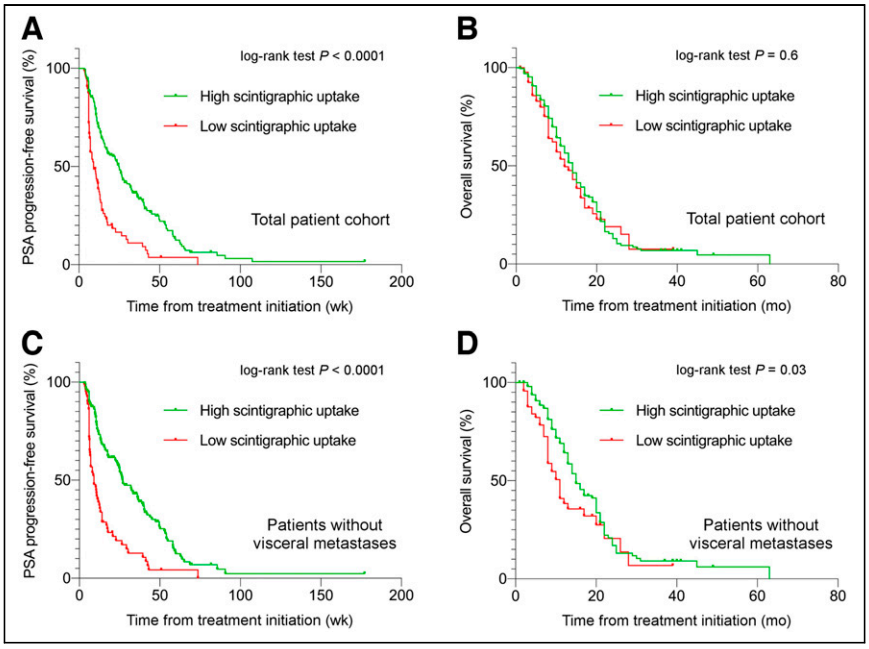

FIGURE 3. Kaplan–Meier survival curves for PSA PFS and OS stratified by high and low uptake on posttherapeutic scintigraphy: PSA PFS (A) and OS (B) in total patient cohort, and PSA PFS (C) and OS (D) in patients without visceral metastases.

(n = 29) of patients with a scintigraphic response, whereas only 29.7% (n = 19) with scintigraphically stable disease and 8.1% (n = 6) with scintigraphic progression achieved a PSA response ($P < 0.0001$; Fig. 4). An example of a patient who showed a scintigraphic response is presented in Figure 5.

The distribution of PSA PFS and OS in patients with a scintigraphic response, stable disease, and progression significantly differed (median, 33.1 vs. 16.0 vs. 9.0 wk [$P < 0.0001$] and 16.5 vs. 11.6 vs. 7.4 mo [$P < 0.0001$], respectively; Figs. 6A and 6B).

Uni- and Multivariable Analysis of Prognostic Factors for Outcome

Univariable Cox regression analysis revealed that rising levels of AP, LDH, PSA, as well as prior chemotherapy and the presence of visceral metastases at baseline, were potential negative prognostic factors for OS, whereas the presence of lymph node–only metastases was a significant positive prognostic factor for OS (Table 2). In multivariable analysis, only rising levels of AP, LDH, and PSA and the presence of visceral metastases were identified as significant prognosticators (Table 2).

High tumor uptake was not associated with OS (P = 0.3) but was associated with longer PSA PFS in both the univariable and the multivariable analyses ($P < 0.0001$ for each) (Supplemental Table 1). Furthermore, scintigraphic progression was negatively associated with OS on both univariable and multivariable analyses ($P < 0.0001$ for each) (Table 3).

DISCUSSION

^{177}Lu-PSMA-I&T is the second most commonly used PSMA-targeted radiopharmaceutical for palliative treatment of mCRPC; however, significantly fewer data have been published for ^{177}Lu-PSMA-I&T than for ^{177}Lu-PSMA-617 so far (*11*). Our retrospective analysis of 301 patients treated with ^{177}Lu-PSMA-I&T substantially expands clinical knowledge about it, underlines its effectiveness, and establishes previously proposed prognostic parameters until the results from the multicenter, randomized prospective phase III trial are published. One important prospective study to which its results might be compared is the SPLASH study (NCT04647526), despite the slight difference in inclusion criteria between that study and ours. Most of our patients also received chemotherapy in addition to second-line hormonal therapy (abiraterone or enzalutamide), contrary to those in SPLASH, who previously received only a single novel androgen receptor axis–targeted therapy but no chemotherapy.

In addition, our analysis underlines the value of PSMA ligand uptake as a noninvasive prognostic imaging biomarker. Specifically, we observed high scintigraphic tumor uptake resulting in a significantly higher PSA response rate and a lower risk of PSA progression. Further, scintigraphic response (defined as a decrease in skeletal infiltration length between 2 cycles) significantly prognosticated a better outcome, with longer PSA PFS and OS.

The number of patients with a 50% PSA decline in our analysis (34%) is well in line with data reported in the literature and, especially, our previous report for ^{177}Lu-PSMA-I&T. A large variation in PSA response rates has been found in the literature, ranging from 20% to 60%, with an estimated PSA response rate of 46% of patients in a recent metaanalysis (*11*). The lower number of PSA responders in our cohort is most likely explained by differences in the patient population. More than two thirds of the patients in our analysis had received chemotherapy before RLT. In univariable analysis, previous exposure to chemotherapy resulted in a 1.5-fold increased risk of death when compared with patients who had not previously received chemotherapy. In the recent metaanalysis by Sadaghiani et al. (*11*),

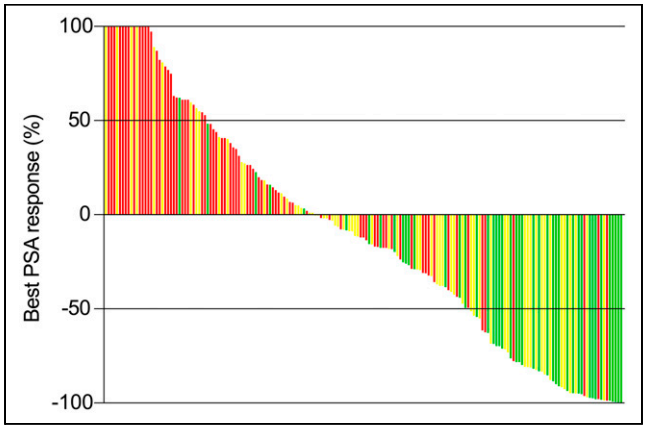

FIGURE 4. Waterfall plot showing response to treatment as measured by serum PSA. Best PSA response is compared with color-coded change in infiltration length on posttherapeutic scintigraphy. First 16 columns represent patients with increase of >100% as best PSA response. Green = patients with response (>0.5 cm decrease in infiltration length between first and second cycles); yellow = stable disease (±0.5-cm change in infiltration length); red = progression (>0.5 cm increase).

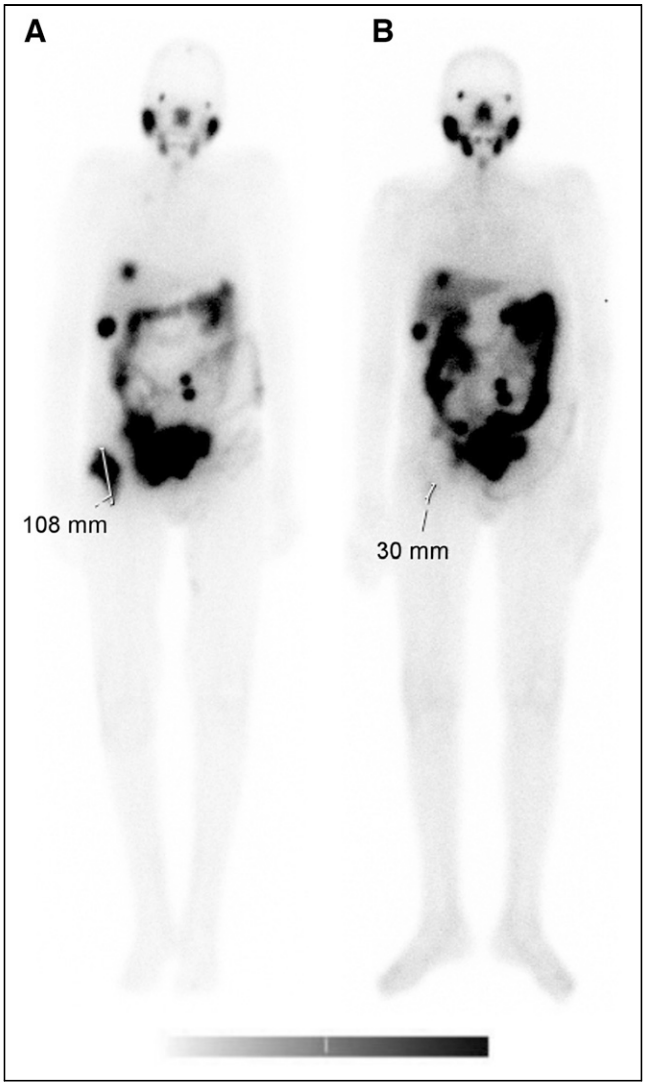

FIGURE 5. (A) An 81-y-old patient with bone, lymph node, and liver metastases presenting with metastatic disease in right femur with extent of 10.8 cm on posttherapeutic whole-body scintigraphy at first cycle of ^{177}Lu-PSMA-I&T. (B) Same patient with decrease in infiltration length to 3.0 cm at second cycle of ^{177}Lu-PSMA-I&T. Change in infiltration length was −7.8 cm, and classification was therefore scintigraphic response. PSA PFS and OS were 24 wk and 22 mo, respectively.

the rate of pretreatment with chemotherapy varied between 0% and 80%. Our data compare well with a retrospective analysis using ^{177}Lu-PSMA-617 RLT in 104 mCRCP posttaxane patients and reporting PSA response in 33% of patients and a median OS of 14 mo (95% CI, 12.6–15.4 mo) (*12*).

Recently, the VISION trial, an international, open-labeled, phase 3 trial evaluating ^{177}Lu-PSMA-617 in patients presenting with mCRPC, was published (*5*). OS was significantly prolonged in patients receiving ^{177}Lu-PSMA-617 as compared with standard care alone (median, 15.3 vs. 11.3 mo; $P < 0.001$). Median OS in our patient cohort receiving ^{177}Lu-PSMA-I&T was slightly shorter, at 13.8 mo (95% CI, 12.4–15.5 mo). However, a substantial number of patients (253/551) in the VISION trial undergoing ^{177}Lu-PSMA-617 RLT had also received androgen-receptor–pathway inhibitors with enzalutamide, abiraterone, or apalutamide as part of the standard of care, which might have some additive effect. In our clinical practice, ^{177}Lu-PSMA-I&T was applied in addition to standard application of gonadotropin-releasing hormone analog but without a combination with other active agents.

In addition, discrepancies between treatment outcome in compassionate-use programs and prospective trials might be further explained by an inconsistency in the applied inclusion criteria. The recently published multicenter, randomized prospective phase II trial TheraP reported a significantly higher treatment response in patients receiving ^{177}Lu-PSMA-617 than in patients receiving cabazitaxel (*4*). However, on the basis of the strict selection criteria, only patients with high ^{68}Ga-PSMA-11 tumor uptake and the absence of ^{18}F-FDG–positive/PSMA ligand–negative lesions were treated. These criteria led to exclusion of 28% of the initially screened patients, with visceral metastases being present in only 7% of the included patient cohort (as compared with 21% of patients in our analysis). The PSA response rate was 66%, compared with 34% in our study.

Our analysis of potential prognostic factors indicated a significant relationship between baseline laboratory parameters (LDH, AP, and PSA) and PSA PFS, and OS, as is in line with previous smaller studies (*13*). However, these findings still remain controversial, and a variety of other reports lack clear associations in multivariable analyses (*14*).

Finally, prior therapy with ^{223}Ra was not associated with a worse outcome of ^{177}Lu-PSMA-I&T therapy. One could assume that β-emitting ^{177}Lu-PSMA-I&T is less effective in tumors that have already progressed after α-emitter treatment, with a much higher linear energy transfer than for ^{177}Lu. However, ^{223}Ra may affect predominantly the tumor stroma because it accumulates in the bone matrix surrounding the cancer cells (*15*). Conversely, ^{177}Lu-PSMA-I&T accumulates directly in prostate cancer cells.

Our data also demonstrate a potential prognostic value of routine posttreatment scintigraphy, as patients with high scintigraphic tumor uptake more frequently achieved PSA response and presented with a reduced risk of PSA progression (PSA PFS, 24.9 vs. 9.0 wk; HR, 0.3; 95%CI, 0.2–0.5; $P < 0.0001$). This finding corroborates a recent retrospective analysis of 50 mCRPC patients showing that high scintigraphic uptake on posttherapeutic scintigraphy was a significant predictor of PSA decline of at least 50% from baseline (OR, 11.77; $P = 0.003$) and PSA PFS (OR, 0.2029; $P = 0.0111$) (*16*). Similarly, Rathke et al. described intense scintigraphic tumor uptake (>salivary gland level) as a significant predictor of partial remission in univariable analysis (OR, 18.0; 95% CI, 2.230–145.3119; $P = 0.0067$) and multivariable analysis (OR, 60.265; 95% CI, 5.038–720.922; $P = 0.001$) (*8*). Tumor response in this analysis was defined by a visual decrease in uptake by metastatic lesions during later treatment cycles, and no correlation with independent clinical outcome parameters (e.g., PSA PFS, and OS) was available. Our analysis adds further data on the potential of scintigraphic tumor uptake to predict OS: no significant reduction in risk of death for patients with high scintigraphic tumor uptake was observed (14.4 vs. 12.4 mo; HR, 0.9; 95% CI, 0.6–1.3; $P = 0.6$). Similar results have recently been published by Hotta et al. (*17*) demonstrating significantly shorter PSA PFS in patients who did not fulfill the VISION criteria but still underwent ^{177}Lu-PSMA-RLT than in those who did fulfill the VISION criteria (2.1 vs. 4.1 mo; HR, 1.6; $P = 0.0025$). Median OS was shorter (9.6 vs. 14.2 mo; HR, 1.4; $P = 0.16$) but not to a statistically significant extent. One potential confounder could be the presence of visceral metastases, which are one of the strongest predictors for OS (*18*). When excluding patients with visceral metastases from our analysis, median OS was significantly longer for high tumor

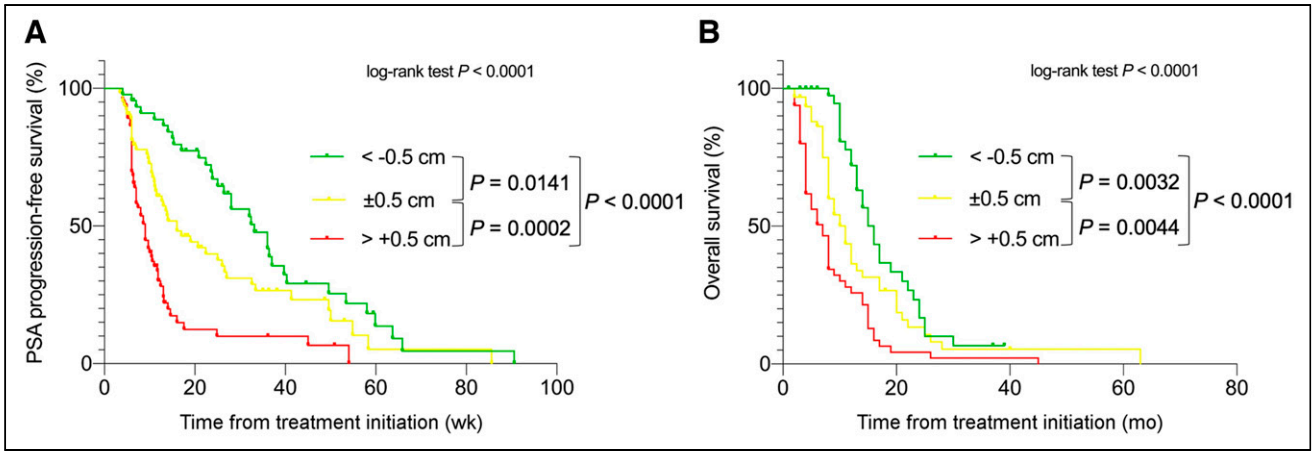

FIGURE 6. Kaplan–Meier survival curves stratified by scintigraphic response (>0.5-cm decrease in infiltration length between first and second cycles), scintigraphically stable disease (±0.5-cm change in infiltration length), and scintigraphic progression (>0.5-cm increase) for PSA PFS (A) and OS (B).

uptake than for low tumor uptake (15.5 vs. 11.4 mo; HR, 0.6; 95% CI, 0.4–1.0; $P = 0.03$).

Pretherapeutic PSMA ligand PET/CT is usually performed to assess whether the patient is eligible for PSMA RLT. Depending on the logistic workflow, there may be a potentially substantial difference in the time to the start of PSMA RLT. Posttherapeutic scintigraphy, usually performed 24 h after injection, offers an intratherapeutic assessment of the disease state and has potential for longitudinal assessment of its changes over time, with no bias due to disease progression in between. Evaluation of posttherapeutic

TABLE 2
Uni- and Multivariable Analysis for Association of Baseline Variables with OS

		Univariable analysis			Multivariable analysis		
Variable	No. of patients	HR	95% CI	*P*	HR	95% CI	*P*
High scintigraphic uptake	295						
No	96	Reference					
Yes	199	0.9	0.6–1.2	0.3	0.8	0.6–1.1	0.2
Age, continuous	295	1.0	1.0–1.0	0.3	1.0	1.0–1.0	0.6
AP per 50 U/L increase, continuous	295	1.0	1.0–1.1	0.0001*	1.0	1.0–1.1	0.02*
LDH per 50 U/L increase, continuous	295	1.0	1.0–1.1	<0.0001*	1.0	1.0–1.1	0.001*
Hemoglobin, continuous	295	1.0	1.0–1.0	0.7	1.0	1.0–1.0	0.4
PSA per 50 ng/mL increase, continuous	295	1.0	1.0–1.0	0.0001*	1.0	1.0–1.0	0.01*
≥2 pretreatments	295						
No	98	Reference					
Yes	197	1.4	1.0–1.9	0.1	1.3	0.8–2.0	0.3
Previous ^{223}Ra	295						
No	254	Reference					
Yes	41	1.0	0.7–1.5	0.9	0.8	0.5–1.2	0.3
Previous chemotherapy	295						
No	84	Reference					
Yes	211	1.5	1.1–2.2	0.02*	1.1	0.7–1.7	0.7
Bone metastases (M1b, without visceral metastases)	211	Reference			Reference		
Lymph node only metastases (N+/M1a)	21	0.3	0.1–0.7	0.007*	0.4	0.2–1.0	0.05
Visceral metastases (M1c)	63	1.5	1.1–2.0	0.03*	1.5	1.0–2.1	0.02*

*Statistically significant.

TABLE 3
Uni- and Multivariable Analysis for Association of Changes in Various Parameters with OS

Change in …	No. of patients	Univariable analysis			Multivariable analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
Infiltration length per 10-mm increase, continuous	182	1.1	1.1–1.3	<0.0001*	1.2	1.1–1.3	<0.0001*
AP per 20% increase, continuous	182	1.0	1.0–1.1	0.13	1.0	1.0–1.1	0.3
LDH per 20% increase, continuous	182	1.2	1.1–1.3	0.001*	1.2	1.0–1.3	0.01*
Hemoglobin per 20% decrease, continuous	182	1.0	0.8–1.4	0.61	1.0	0.8–1.4	0.8
PSA per 20% increase, continuous	182	1.0	1.0–1.1	0.03*	1.0	1.0–1.0	0.8

*Statistically significant.

scintigraphy is easy to apply and has the potential to yield a useful imaging biomarker for prognosticating treatment outcome.

Finally, we present the extent of disease in the appendicular skeleton on posttherapeutic scintigraphy and its change between the first and second treatment cycles as a potential simple and quickly assessable new biomarker. Patients with a scintigraphic response (defined as a decrease in skeletal infiltration length between 2 cycles) presented with a significantly higher likelihood for a PSA response (64.4%), a significantly longer median PSA PFS (33.1 wk), and a longer median OS (16.5 mo). Moreover, whereas whole-body posttreatment scans allow detection of suggestive tumor uptake from head to toe and therefore enable a potentially powerful and inexpensive way to monitor tumor response, pretherapeutic PET/CT imaging is usually performed from skull base to mid thigh (skull and extremities are not included routinely) and is not suitable for routine assessment of the extent of disease in the appendicular skeleton.

Our study had several limitations, including the retrospective nature of the analysis. Qualitative evaluation of scintigraphic uptake and quantitative measurement of skeletal involvement are prone to potential error. However, all posttherapeutic scintigrams were analyzed and measured by the same reader, providing consistency within our patient cohort. Nevertheless, future studies also analyzing interreader agreement are warranted. Finally, the proposed biomarker of scintigraphic response as defined in this analysis is applicable only to patients with metastases in the appendicular skeleton and should be expanded to other organ systems in the future.

CONCLUSION

Our retrospective analysis of a large cohort of consecutive mCRPC patients undergoing ^{177}Lu-PSMA-I&T corroborates previous clinical data on treatment efficacy. It establishes known clinical and laboratory prognostic factors, such as the presence of visceral metastases, elevated LDH, and elevated AP. The clear association between PSA PFS and OS and posttreatment scintigraphic tumor uptake underlines the value of PSMA expression as a prognostic indicator. Finally, we propose skeletal tumor extent on posttherapeutic scintigraphy as a potential novel and simple prognostic imaging biomarker that should be explored in further prospective studies.

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 it possible to predict patient outcome using clinical and laboratory parameters and newly proposed posttreatment whole-body scintigraphy parameters updating our experience in a large number of consecutive mCRPC patients?

PERTINENT FINDINGS: Our retrospective analysis on a large number of mCRPC patients undergoing ^{177}Lu-PSMA-I&T corroborated previous reports on ^{177}Lu-PSMA-617 considering PSA response, PSA PFS, and OS. Moreover, it significantly established known prognostic factors, such as the presence of visceral metastases, elevated LDH, and elevated AP, and introduced tumor extent in the appendicular skeleton on posttherapeutic scintigraphy as a significant imaging biomarker predicting patient outcome.

IMPLICATIONS FOR PATIENT CARE: Our retrospective analysis might pave the way for widespread use and better patient selection of ^{177}Lu-PSMA-I&T in mCRPC patients and potentially introduces a simple and inexpensive imaging tool for tumor response assessment.

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