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^{177}Lu-PSMA-I&T for treatment of metastatic castration resistant prostate cancer: prognostic value of scintigraphic and clinical biomarkers

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ABSTRACT

Purpose: The aim of this retrospective analysis was to determine prostate specific antigen (PSA) response, PSA-progression free and overall survival (PSA-PFS and OS) of 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:** A total of 301 consecutive mCRPC patients were included in this analysis. Prognostic factors included clinical parameters, routine laboratory parameter as well as findings on post-treatment scintigraphy. Scintigraphic tumor uptake of ^{177}Lu-PSMA-I&T was compared with salivary gland uptake and classified as high and low. The extent of skeletal metastatic disease was estimated by measuring its longest extent and its changes during therapy were used to define scintigraphic progression, response and stable disease. PSA response ≥50%, PSA-PFS and OS were calculated. **Results:** In total 1138 cycles (median of 3 cycles per patient) of ^{177}Lu-PSMA-I&T using a standard activity of 7.4 GBq were applied intravenously every 4-10 weeks (median 6 weeks). Overall 34% (95% CI, 28%-38%) of patients showed a PSA response ≥50% and median PSA-PFS and OS of the total patient cohort were 16.0 weeks (95% CI, 12.1-19.9) and 13.8 months (95% CI, 12.4-15.5), respectively. Patients with high scintigraphic tumor uptake showed a higher PSA response rate ≥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 weeks, HR 0.3, 95% CI, 0.2-0.5; $p<0.0001$). In our data risk of death was not significantly different in patients with high scintigraphic uptake compared to low scintigraphic uptake (medians 14.4 vs. 12.4 months, HR 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 one treatment cycle. **Conclusions:** 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.

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

INTRODUCTION

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 two phase II prospective trials *(1,3,4)*. Recently prolonged overall survival (OS) and progression-free-survival (PFS) was proven in a randomized phase III clinical trial just recently resulting in FDA approval *(5)*. Further, clinical parameters such as a 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)*. LuPSMA I&T is currently 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 PSA decline of ≥50% within 12 weeks 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.

First preliminary retrospective analyses indicate that intensity on post-therapeutic ^{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 its impact on overall survival (OS) has not been evaluated. Based on our clinical experience, the extent of disease and specifically the infiltration of the appendicular skeleton in post-therapeutic scans and its change

during ^{177}Lu-PSMA RLT also holds promise to serve as a new and potentially prognostic imaging biomarker.

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

MATERIALS AND METHODS

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

301 consecutive mCRPC patients, receiving at least two cycles of ^{177}Lu-PSMA-I&T between December 2014 and July 2020 were included in this retrospective analysis. All patients had previously received second-line hormonal therapy with abiraterone and/or enzalutamide and chemotherapy or were unfit for chemotherapy. Patient characteristics are shown in Table 1. Prior 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 were treated. Of note, this patient population includes the 100 patients reported by Heck et al. but adds new patients as well as 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 (AMG §13 2b). The institutional ethics committee approved this retrospective analysis under the reference number 115/18S and all subjects signed a 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

Post-therapeutic whole-body scintigraphy (planar anterior and posterior) was acquired approximately 24 h p.i. at every cycle using a Symbia-T-series camera with medium energy parallel collimator, a scan speed of 20 cm/min and 113 keV ±20% and 208 keV ±12% photo peak window. All images were evaluated by one nuclear medicine physician in training under the supervision of a board-certified nuclear medicine physician with >7 years 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 post-treatment scan was visually classified as "high scintigraphic uptake" when the majority of metastatic lesions exceeded the physiological uptake of the salivary glands. If tumor uptake of the majority of lesions was equal to or lower than the uptake in the salivary glands, the patient was classified as "low scintigraphic uptake". The extent of skeletal metastatic disease was assessed by a simple quantitative index: 1. In the 1st post-therapy scintigraphy the longest extent of metastatic disease in one single bone (for example femur) contributing to the appendicular skeleton (including clavicula, scapula, humerus, radius/ulna, the pelvic bones except the sacrum, femur, tibia/fibula) was identified and its absolute extent was quantified using a ruler measurement. In case with discontinuous metastatic bone infiltration in a particular bone, the extents of metastatic disease were each measured and summed up. 2. In the 2nd post-therapy scintigraphy the extent of the same metastatic site was reassessed. 3. The absolute change between the 1st and 2nd post-therapeutic scan was calculated and defined as Δinfiltration length. 4. Scintigraphic progression, response and stable disease were defined as >0.5cm increase, >0.5cm decrease and ±0.5cm change in infiltration length between the 1st and 2nd cycle, respectively.

Clinical parameters, PSA response and PSA progression

The following pre-therapeutic parameters were collected: age, alkaline phosphatase (AP), LDH, hemoglobine (Hb), prostate specific antigen (PSA) and its relative changes (ΔAP, ΔLDH, ΔHb, ΔPSA) between the 1st and 2nd cycle. PSA response was defined as PSA decline ≥50% from baseline according to Prostate Cancer Clinical Trials Working Group 3 *(9)*. PSA progression was either defined as PSA increase ≥25% and ≥2 ng/ml above the nadir after initial PSA decline or PSA increase ≥25% and ≥2 ng/ml from baseline in case with no PSA decline *(9)*.

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

Statistical analysis

Primary outcome measures were PSA response, OS and PSA-progression-free survival (PSA-PFS). Kaplan-Meier method was used for estimation of event time distributions and logrank tests were used for group comparisons. To correct for log-rank test alpha error accumulation, significance was assumed when $p < 0.016$ (Bonferroni correction for impact of infiltration length on OS and PSA-PFS). Frequencies of PSA response were compared between groups using Chi-square tests.

Univariable and multivariable Cox regression analyses were performed to determine the association of pre-therapeutic parameters, relative changes of laboratory parameters and information from post-therapeutic scintigraphy (scintigraphic tumor uptake and Δinfiltration 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 (HR) and 95% confidence intervals (CI) are presented. A *p* value of <0.05 was considered statistically significant.

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

Chi-square tests, Kaplan-Meier estimation, logrank tests and calculation of Cohen´s kappa coefficient were performed using GraphPad Prism version 8.4.3 for MAC (GraphPad Software, San Diego, California USA, www.graphpad.com). Uni- and multivariable Cox regression analysis were performed using IBM SPSS Statistics for Windows Version 25.0. (Armonk, NY: IBM Corp.).

RESULTS

A total number of 301 patients have been analyzed. In total 1138 cycles of PSMA RLT with a median of 3 cycles per patient (range 2-20) were applied. Patients received an intravenous treatment using a standard activity of 7.4 GBq ^{177}Lu-PSMA-I&T every 4–10 weeks (median 6 weeks) which could be slightly adopted based on e.g. lab test and tumor burden. Median time on treatment was 3 months. Post-therapeutic scintigraphies and complete laboratory results were not available in two and four patients, respectively. At baseline pelvic lymph nodes, extrapelvic lymph nodes, bone and visceral metastases were present in 159 (52.8%), 192 (63.8%), 274 (91.0%) and 64 (21.3%) patients, respectively. Median follow-up time was 9 months (range 1-63 months). 101 (34%, 95% CI, 28%-38%) patients achieved PSA response following PSMA targeted RLT. In the total patient cohort median OS was 13.8 months (95% CI, 12.4-15.5) and median PSA-PFS was 16.0 weeks (95% CI, 12.1-19.9). At the time of analysis 226 patients had shown PSA progression and 182 patients had deceased.

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 in high and low scintigraphic tumor uptake achieved substantial agreement for intra-rater reliability (*k*: 0.796). PSA response was achieved in 91 (45.7%) patients with high scintigraphic tumor uptake vs. 10 (10.4%) patients with low scintigraphic tumor uptake ($p<0.0001$; Figure 1). Example of patients with high and low scintigraphic tumor uptake are presented in Figure 2.

PSA-PFS in patients with high scintigraphic tumor uptake was significantly longer than those presenting with low uptake (medians 24.9 weeks vs. 9.0 weeks; HR 0.3, 95% CI, 0.2-0.5; $p<0.0001$; Figure 3A). OS was not significantly different in patients with high scintigraphic uptake compared to low scintigraphic uptake (medians 14.4 months vs. 12.4 months; HR 0.9, 95% CI, 0.6-1.3; $p=0.6$; Figure 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 compared to low scintigraphic tumor uptake (medians 26.7 weeks vs. 9.0 weeks; HR 0.3, 95% CI, 0.2-0.4; $p<0.0001$ and 15.5 months vs. 11.4 months; HR 0.6, 95% CI, 0.4-1.0; $p=0.03$, respectively; Figure 3C and 3D).

Impact of infiltration length on PSA response, PSA-PFS and OS

The median extent of the metastases on the first and second post-treatment scan were 9.8 cm (range 1.2-76.9 cm) and 10.3 cm (range 0.0-78.4 cm), respectively. In four patients the extent of metastatic disease in femur and tibia/fibula were summed up due to 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 (Supplementary Figure 1).

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 intra-rater reliability (weighted *k*: 0.711). PSA response was achieved in 64.4% (n=29) of patients presenting with scintigraphic response, while only 29.7% (n=19) with scintigraphic stable disease and 8.1% (n=6) of patients with scintigraphic progression achieved PSA response ($p<0.0001$; Figure 4). An example of a patient who showed scintigraphic response is presented in Figure 5.

Distribution of PSA-PFS and OS of patients with scintigraphic response, stable disease and progression were significantly different (medians 33.1 vs. 16.0 vs. 9.0 weeks; $p<0.0001$ and 16.5 vs. 11.6 vs. 7.4 months; $p<0.0001$, respectively; Figure 6A and 6B).

Uni- and multivariable analysis of prognostic factors for outcome

Univariable Cox regression analysis revealed rising levels of AP, LDH, PSA as well as prior chemotherapy and the presence of visceral metastases at baseline as potential negative prognostic factors for OS, while 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, PSA and the presence of visceral metastases were identified as significant prognosticators (Table 2).

High scintigraphic tumor uptake was not associated with OS ($p=0.3$), however, it was associated with longer PSA-PFS both in the uni- and multivariable analysis ($p<0.0001$ each, respectively) (Supplementary Table 1). Furthermore, scintigraphic progression was negatively associated with OS on both uni- and multivariable analysis (both $p<0.0001$) (Table 3).

DISCUSSION

^{177}Lu-PSMA-I&T is the second most commonly used PSMA targeted radiopharmaceutical for palliative treatment of mCRPC, however, significantly less data have been published so far *(11)*. Our retrospective analysis of 301 patients treated with ^{177}Lu-PSMA-I&T substantially expands its clinical knowledge, underlines the effectiveness of ^{177}Lu-PSMA-I&T 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 its inclusion criteria slightly differ from patients included in our retrospective analysis. Most of our patients have also received chemotherapy in addition to second-line hormonal therapy (abiraterone and/or enzalutamide) contrary to those in SPLASH previously receiving only one novel androgen receptor axis-targeted therapy but no chemotherapy.

In addition, our analysis underlines the value of PSMA-ligand uptake as non-invasive prognostic imaging biomarker. Specifically, we have 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 decrease of skeletal infiltration length between two cycles) significantly prognosticated better outcome with longer PSA-PFS and OS.

The number of patients with 50% PSA decline in our analysis (34%) is well in line with data reported in literature and especially our previous report for ^{177}Lu-PSMA-I&T. A large variation of PSA-response rates have been published in literature ranging from 20 to 60% with an estimated PSA-response rate of 46% patients in a recent meta-analysis *(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 have received chemotherapy prior to RLT. In univariable analysis previous exposure to chemotherapy resulted in a 1.5-fold higher risk of death when compared to patients who had not previously received chemotherapy. In the recent meta-analysis by Sadaghiani et al. the rate of pre-treatment with chemotherapy varies between 0 and 80%. Our data compare well with a retrospective analysis using ^{177}Lu-PSMA-617 RLT in 104 mCRCP post-taxane patients and reporting PSA-response in 33% of patients and a median overall survival of 14 months (95% CI, 12.6-15.4 months) *(12)*.

Recently, the VISION trial, an international, open-labelled, 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 of 15.3 vs. 11.3 months; $p<0.001$). Of note, median OS in our patient cohort receiving ^{177}Lu-PSMA I&T was slightly shorter with 13.8 months (95% CI, 12.4-15.5). However, a substantial number of patients (253/551) in the VISION-trial undergoing ^{177}Lu-PSMA-617 RLT have also received androgen-receptor–pathway inhibitors with enzalutamide, abiraterone, or apalutamide as part of 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 GnRH-analoga but without a combination with other active agents.

In addition, discrepancies between treatment outcome in compassionate use programs and prospective trials could potentially be further explained by an inconsistency in the applied inclusion criteria. The recently published, prospective, multi-center, randomized Phase II trial TheraP reported a significantly higher treatment response in patients receiving ^{177}Lu-PSMA-617 versus cabazitaxel *(4)*. However, based on 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 lead to the exclusion of 28% of the initially screened patients with visceral metastases being only present in 7% of the included patient cohort (as compared to 21% patients in our analysis). PSA response rate was 66% compared to 34% reported in our study, respectively.

Our analysis of potential prognostic factors indicated a significant relationship between baseline laboratory parameters (LDH, AP, and PSA) and PSA-PFS and OS which 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 Radium-223 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 which have already progressed after alpha-emitter treatment with a much higher linear energy transfer compared to ^{177}Lu. However, Radium-223 may predominantly affect the tumor stroma as it is accumulated in the bone matrix surrounding the cancer cells *(15)*. Conversely, ^{177}Lu-PSMA-I&T is directly accumulated by the prostate cancer cells.

Our data also demonstrate a potential prognostic value of routine post-treatment 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 weeks; HR 0.3, 95%CI, 0.2-0.5, $p<0.0001$). This corroborates a recent retrospective analysis of 50 mCRPC patients showing that high scintigraphic uptake on post-therapeutic scintigraphy was a significant predictor of PSA decline ≥50% from baseline (OR 11.77; $p=0.003$) and PSA-PFS (OR 0.2029; $p=0.0111$) *(16)*. Similar, Rathke et al. described intense scintigraphic tumor uptake (above salivary gland level) as significant predictor of partial remission in uni- (OR 18.0, 95% CI, 2.230–145.3119; $p=0.0067$) and multivariable analyses (OR 60.265, 95% CI, 5.038–720.922; $p=0.001$) *(8)*. Of note,

tumor response in this analysis was defined by visual decrease of tracer uptake by metastatic lesions during later treatment cycles and no correlation with independent clinical outcome parameters (e.g. PSA-PFS and OS) were available. Our analysis adds further data on the potential of scintigraphic tumor uptake to predict OS: No significant reduction of risk of death for patients with high scintigraphic tumor uptake was observed (14.4 vs. 12.4 months; HR 0.9, 95% CI, 0.6-1.3, p=0.6). Similar results have been recently published by Hotta et al. *(17)* demonstrating significantly shorter PSA-PFS in patients who did not fulfill the VISION-criteria but still underwent LuPSMA RLT compared to those who did (2.1 vs. 4.1 months, HR 1.6; p=0.0025). Median OS was shorter (9.6 mo vs. 14.2 mo, HR 1.4; p=0.16), but failed statistical significance. One potential confounder could be the presence of visceral metastases which is one of the strongest predictors for OS *(18)*. When excluding patients with visceral metastases in our analysis median OS was significantly longer for high vs. low scintigraphic tumor uptake (15.5 months vs. 11.4 months; HR 0.6, 95% CI, 0.4-1.0, p=0.03).

The pretherapeutic PSMA-ligand PET/CT imaging is usually performed to assess the eligibility of the patient to undergo PSMA RLT. Depending on the logistical workflow a potentially substantial time difference to the start of PSMA RLT might be present. Post-therapeutic scintigraphy usually performed 24 hours after injection offers an intra-therapeutic assessment of the disease state with the potential of longitudinal assessment of its changes over time with no potential bias due to disease progression in-between. The evaluation of post-therapeutic scintigraphy is easy to apply and has the potential to yield an useful imaging biomarker for prognosticating treatment outcome.

Finally, we present the extent of disease in the appendicular skeleton on post-therapeutic scintigraphy and its change between first and second treatment cycle as potential new, simple and quickly to assess biomarker. Patients with a scintigraphic response (defined as decrease of skeletal infiltration length between two cycles) presented with a significantly higher likelihood for a PSA response (64.4%), a significantly longer median PSA-PFS (33.1 weeks) and longer median OS (16.5 months). Moreover, while whole-body post-treatment scans allow the detection of suspicious 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 the assessment of the extent of disease in the appendicular skeleton on a routine basis.

Our study has several limitations including the retrospective nature of this analysis. The qualitative evaluation of scintigraphic uptake and quantitative measurement of the skeletal involvement is prone to potential errors. However, all post-therapeutic scintigraphies 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 only applicable 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 AP. The clear association between PSA-PFS and OS and post-treatment scintigraphic tumor uptake underlines the value of PSMA-expression as prognostic indicator. Finally, we propose the skeletal tumor extent on post-therapeutic scintigraphy as potential novel and simple prognostic imaging biomarker which should be explored in further prospective studies.

KEY POINTS:

Question: Is it possible to predict patient outcome using clinical and laboratory parameters as well as newly proposed post-treatment whole-body scintigraphy parameters updating our experience in a large number of consecutive mCRPC patients?

Pertinent findings: Our retrospective analysis in a large number of mCRPC patients undergoing ^{177}Lu-PSMA-I&T corroborates previous reports on ^{177}Lu-PSMA-617 considering PSA response, PSA progression free survival and overall survival. Moreover, it significantly establishes known prognostic factors, such as the presence of visceral metastases, elevated LDH and AP and introduces tumor extent in the appendicular skeleton on post-therapeutic scintigraphy as a significant imaging biomarker predicting patient outcome.

Implications for patient: Our retrospective analysis could 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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Table 1 Baseline patient characteristics

No. of patients	301
Age (yr), median (IQR), n = 301	73 (67-77)
PSA (ng/ml), median (IQR), n = 297	99.5 (20.4-290.3)
LDH (U/l), median (IQR), n = 297	263.5 (218-344)
AP (U/l), median (IQR), n = 297	112 (72-231)
Hb (g/dl), median (IQR), n = 297	11.7 (10.3-12.8)
Prior systemic therapies for mCRPC, no., n=301	
Docetaxel	213
Cabazitaxel	48
Abiraterone	252
Enzalutamide	183
^{223}Radium	41
Previous chemotherapy	214
No. of prior mCRPC therapies, no., n=301	
1	105
2	109
3	68
4	18
5	4
Site of metastasis, no., 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

AP alkaline phosphatase, Hb hemoglobin, LDH lactate dehydrogenase, PSA prostate-specific antigen

Table 2 Uni- and multivariable analysis for the association of baseline variables with OS

		Univariable analysis			Multivariable analysis		
	No. of pts	HR	95% CI	*p* value[a]	HR	95% CI	*p* value[a]
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**
Hb 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 radium-223	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							
Yes	84	Reference					
	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**

AP alkaline phosphatase, CI confidence interval, Hb hemoglobine, HR hazard ratio, LDH lactate dehydrogenase, PSA prostate-specific antigen

[a] Significant p values are given in bold

Table 3 Uni- and multivariable analysis for the association of changes in various parameters with OS

		Univariable analysis			Multivariable analysis		
	No. of pts	HR	95% CI	*p* value[a]	HR	95% CI	*p* value[a]
Δinfiltration_length per 10 mm increase Continuous	182	1.1	1.1-1.3	**<0.0001**	1.2	1.1-1.3	**<0.0001**
ΔAP per 20% increase Continuous	182	1.0	1.0-1.1	0.13	1.0	1.0-1.1	0.3
ΔLDH per 20% increase Continuous	182	1.2	1.1-1.3	**0.001**	1.2	1.0-1.3	**0.01**
ΔHb per 20% decrease Continuous	182	1.0	0.8-1.4	0.61	1.0	0.8-1.4	0.8
ΔPSA per 20% increase Continuous	182	1.0	1.0-1.1	**0.03**	1.0	1.0-1.0	0.8

ΔAP delta alkaline phosphatase, CI confidence interval, Δinfiltration_length intratherapeutic change of infiltration length, ΔHb delta hemoglobine, HR hazard ratio, ΔLDH delta lactate dehydrogenase, ΔPSA delta prostate-specific antigen

[a] Significant *p* values are given in bold

Figure 1 Waterfall plot showing response to treatment as measured by serum PSA. Best PSA response, defined as the smallest increase or greatest decrease in PSA from baseline compared with color coded ^{177}Lu-PSMA-ligand uptake in post-therapeutic whole-body scintigraphy (p.t.-scintigraphic). Red = Patients with low scintigraphic uptake in p.t.-scinitigraphy. Green = Patients with high scintigraphic uptake in p.t.-scintigraphy. First 21 columns represent patients with an increase of >100% as the best PSA response.

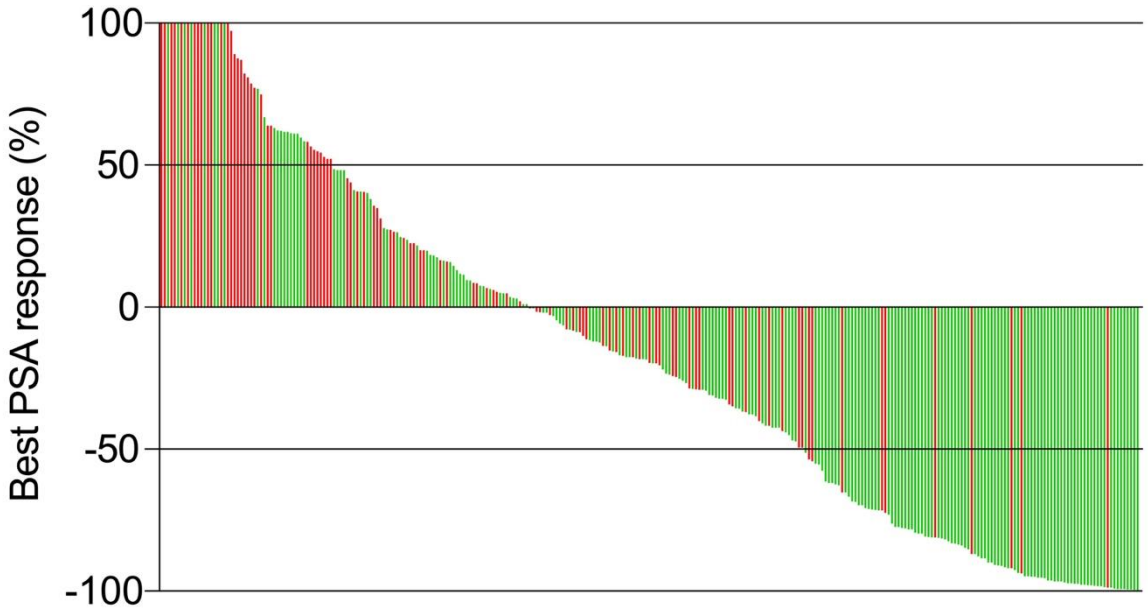


Figure 2 (A) 69-year old patient with bone metastases presenting with high scintigraphic uptake and (B) 76-year old patient with bone and lymph node metastases presenting with low scintigraphic uptake in post-therapeutic whole-body scintigraphy at the 1st cycle of ^{177}Lu-PSMA-I&T. PSA-PFS and OS were 58 weeks and 24 months in patient (A) and 17 weeks and 10 months in patient (B), respectively.

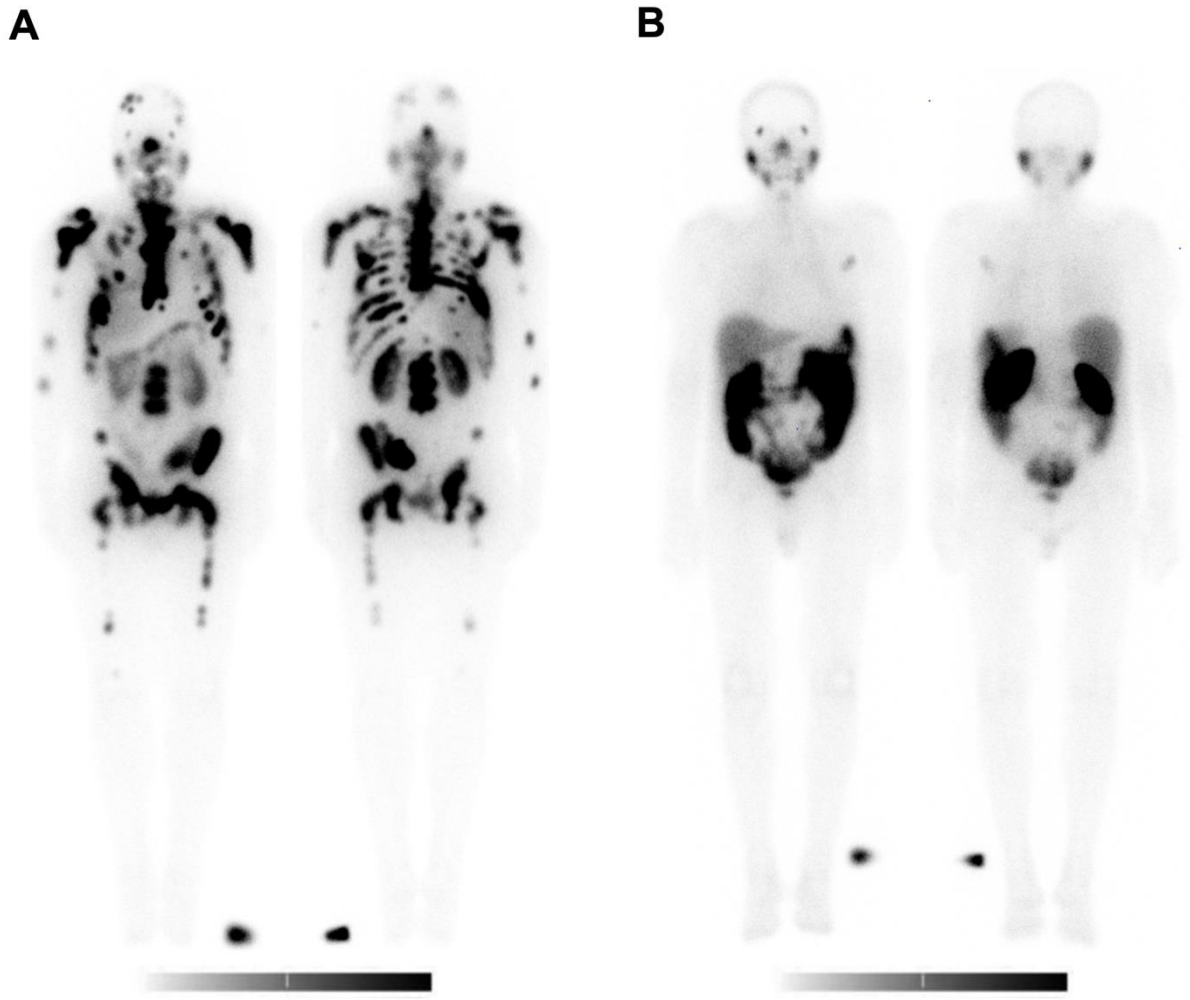


Figure 3 Kaplan-Meier survival curves for PSA progression-free survival (PSA-PFS) and overall survival (OS) stratified by high and low scintigraphic uptake on post-therapeutic scintigraphies. (A) and (B) PSA-PFS and OS in the total patient cohort. (C) and (D) PSA-PFS and OS in patients without visceral metastases.

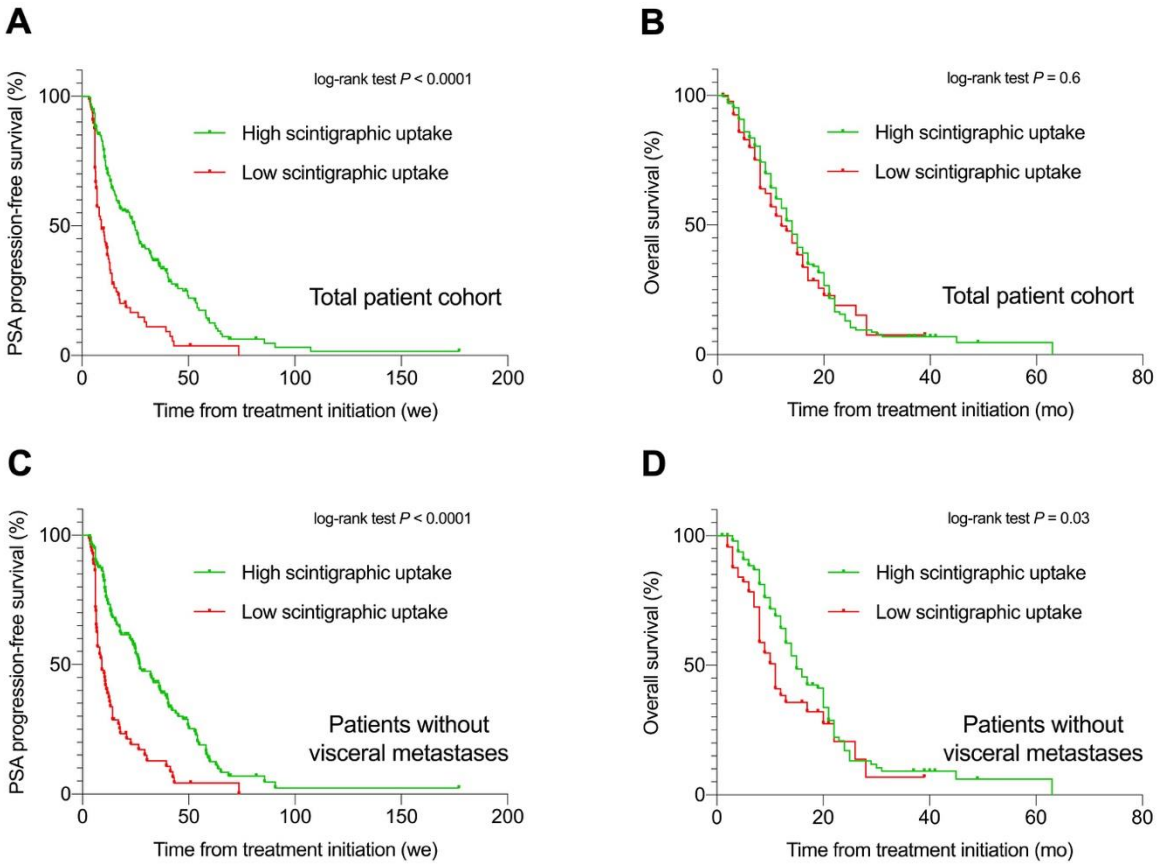


Figure 4 Waterfall plot showing response to treatment as measured by serum PSA. Best PSA response compared with color coded Δinfiltration length in p.t.-scintigraphy. Green = Patients with response (>0.5cm decrease in infiltration length between the 1st and 2nd cycle). Yellow = stable disease (±0.5cm change in infiltration length). Red = progression (>0.5cm increase). First 16 columns represent patients with an increase of >100% as the best PSA response.

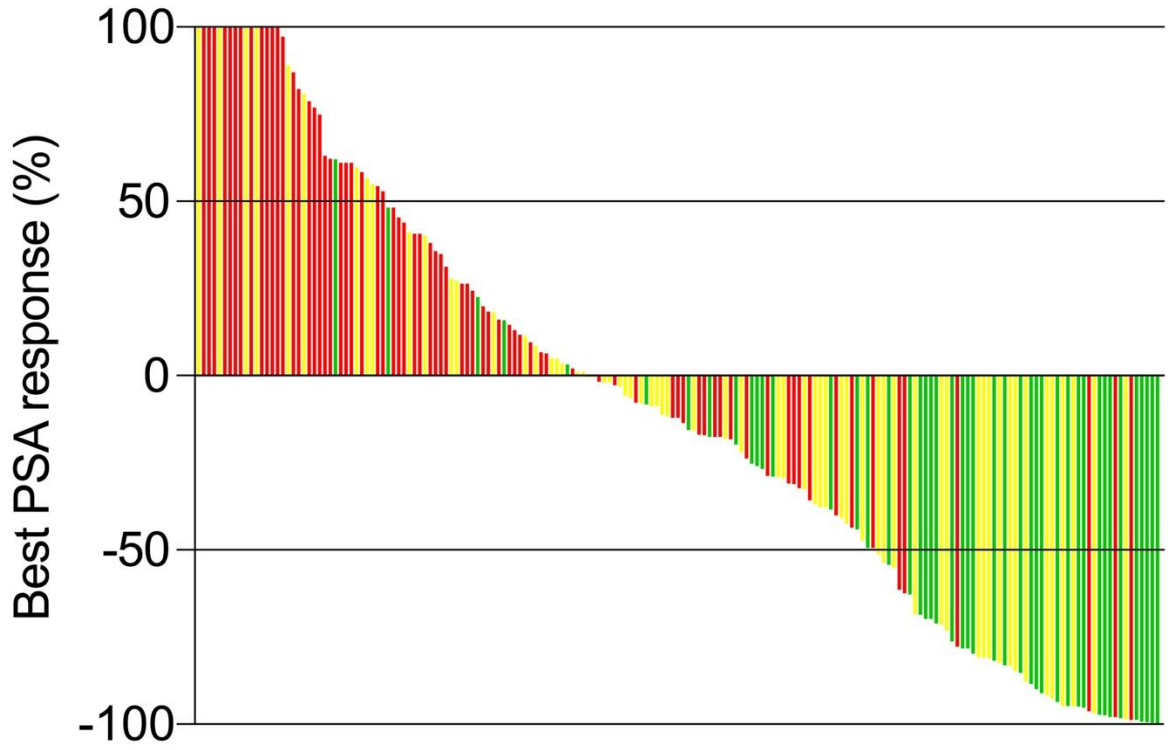


Figure 5 (A) 81-year old patient with bone, lymph node and liver metastases presenting with a metastatic disease in the right femur with an extent of 10.8 cm in post-therapeutic whole-body scintigraphy at the 1st cycle of ^{177}Lu-PSMA-I&T and (B) same patient with a decrease in infiltration length to 3.0 cm at the 2nd cycle of ^{177}Lu-PSMA-I&T. Δinfiltration length of -7.8 cm and therefore classification as scintigraphic response. PSA-PFS and OS were 24 weeks and 22 months, resepectively.

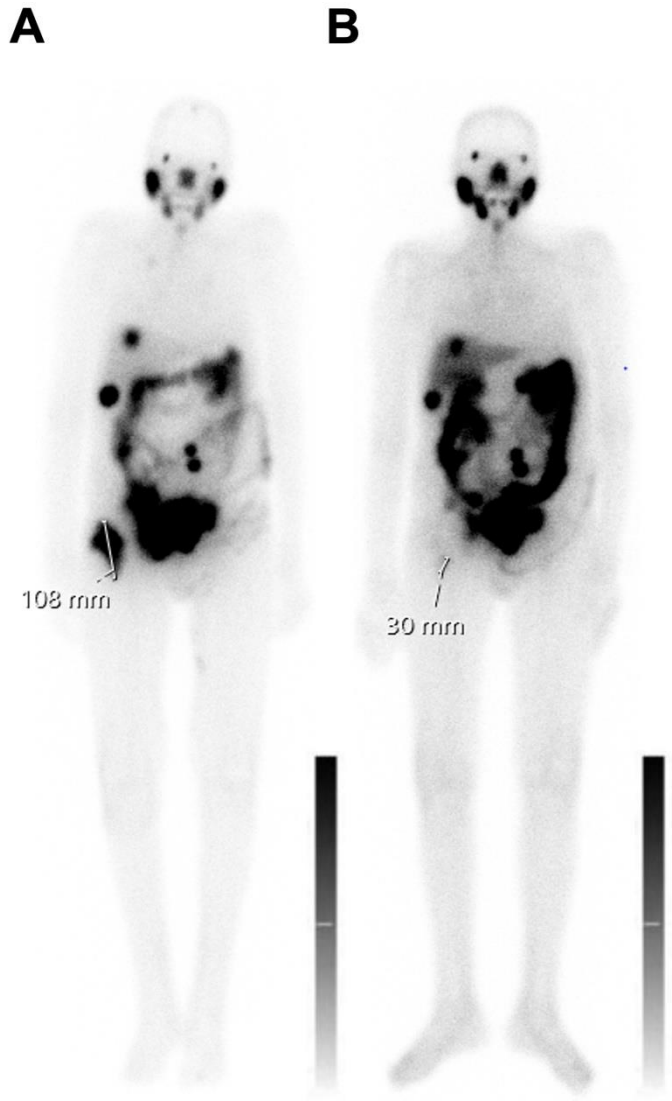
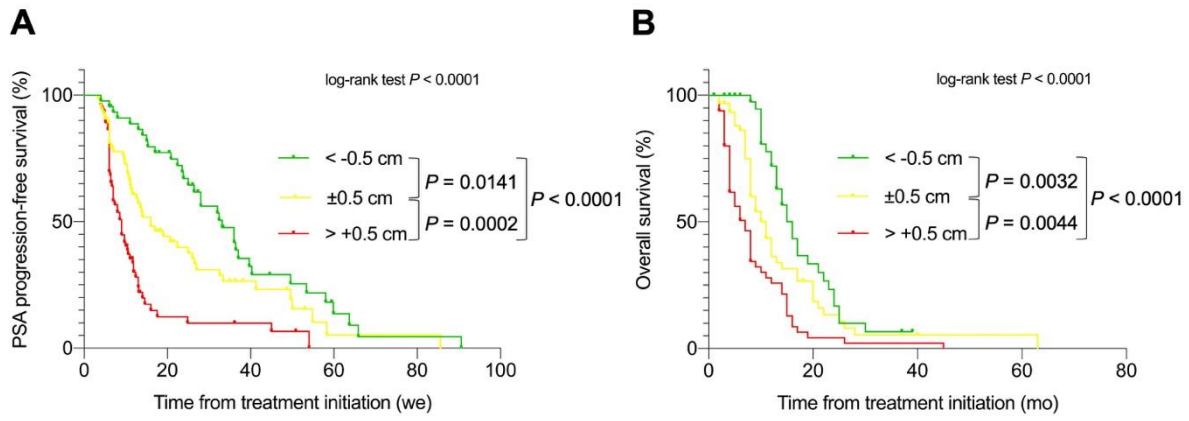
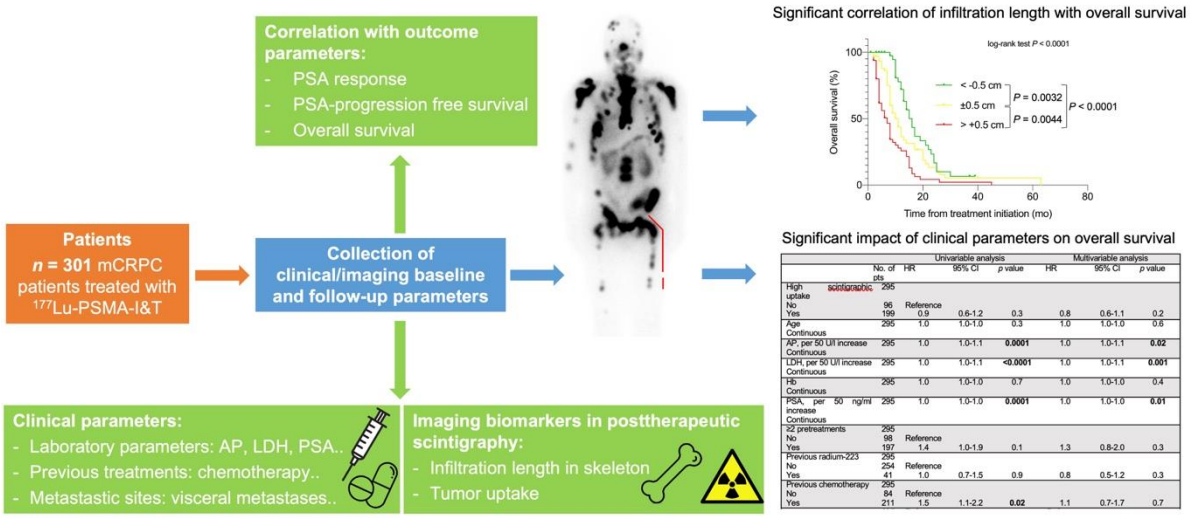


Figure 6 Kaplan-Meier survival curves stratified by scintigraphic response (>0.5 cm decrease in infiltration length between the 1st and 2nd cycle), scintigraphic stable disease (±0.5 cm change in infiltration length) and scintigraphic progression (>0.5 cm increase) for (A) PSA progression-free survival and (B) overall survival. Δinfiltration length = change of infiltration length between the 1st and 2nd cycle.



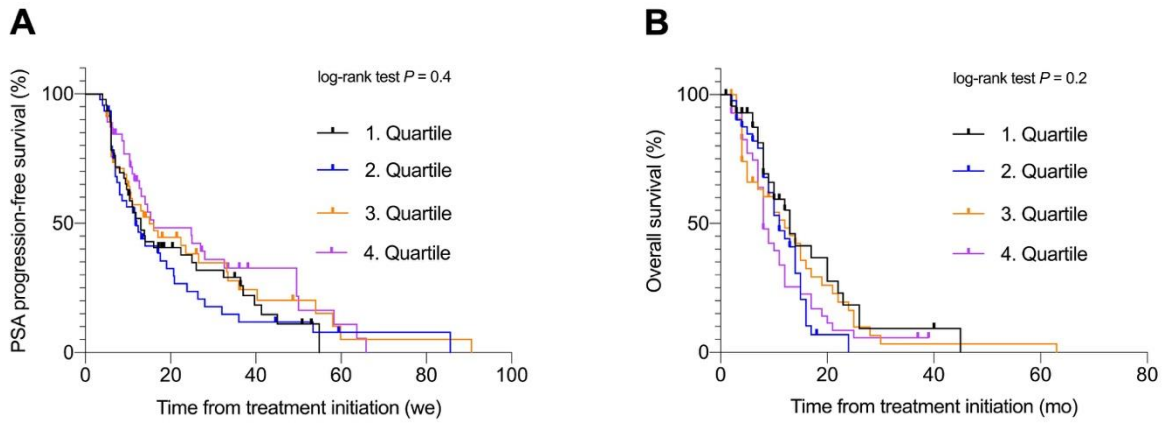
Graphical Abstract



Significant impact of clinical parameters on overall survival

	No. of pts	HR	95% CI	*p* value	HR	95% CI	*p* value
			Univariable analysis			Multivariable analysis	
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**
Hb 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 radium-223	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

Supplementary Figure 1 Kaplan-Meier survival curves stratified by quartiles of longest infiltration length in the appendicular skeleton after 1st cycle of ^{177}Lu-PSMA-I&T for (A) PSA-PFS and (B) OS.



Supplementary Table 1: Uni- and multivariable analysis for the association of baseline variables with PSA-PFS

		Univariable analysis			Multivariable analysis		
	No. of pts	HR	95% CI	*p* value[a]	HR	95% CI	*p* value[a]
High scintigraphic uptake	295						
No	96	Reference					
Yes	199	0.4	0.3-0.6	**<0.0001**	0.3	0.2-0.5	**<0.0001**
Age Continuous	295	1.0	1.0-1.0	**0.04**	1.0	1.0-1.0	0.9
AP, per 50 U/l increase Continuous	295	1.0	1.0-1.1	**0.04**	1.0	1.0-1.1	0.3
LDH, per 50 U/l increase Continuous	295	1.0	1.0-1.0	**0.002**	1.0	1.0-1.1	**0.003**
Hb Continuous	295	1.0	0.9-1.0	0.21	1.0	0.9-1.1	0.8
PSA, per 50 ng/ml increase Continuous	295	1.0	1.0-1.0	0.9	1.0	1.0-1.0	0.3
≥2 pretreatments	295						
No	98	Reference					
Yes	197	1.6	1.2-2.1	**0.003**	1.4	1.0-2.1	0.1
Previous radium-223	295						
No	254	Reference					
Yes	41	0.9	0.6-1.4	0.7	0.9	0.6-1.3	0.6
Previous chemotherapy	295						
No	84	Reference					
Yes	211	1.9	1.4-2.5	**0.0001**	1.6	1.1-2.5	**0.03**
Bone metastases (M1b, without visceral metastases)	211	Reference			Reference		
Lymph node only metastases (N+/M1a)	21	0.5	0.3-0.9	**0.02**	0.6	0.3-1.0	0.1
Visceral metastases (M1c)	63	1.4	1.0-1.9	**0.07**	1.3	1.0-1.9	0.1

AP alkaline phosphatase, CI confidence interval, Hb hemoglobine, HR hazard ratio, LDH lactate dehydrogenase, PSA prostate-specific antigen

[a] Significant p values are given in bold