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Lutetium-177 PSMA Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy

Short-running title / foot line: Lu-177 PSMA: Safety and Efficacy

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ABSTRACT

Aim: The objective of this study was to analyze the safety and efficacy of ^{177}Lu-labeled DOTAGA-based prostate specific membrane antigen (PSMA) ligand ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE) (^{177}Lu-PSMA) in patients with metastatic castration-resistant prostate cancer (mCRPC).

Methods: Fifty-six mCRPC patients underwent PSMA radioligand therapy (RLT) with ^{177}Lu-PSMA. ^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA) PET/CT was used for patient selection and follow-up after PSMA-RLT. Hematological status, renal function and serum prostate specific antigen (PSA) levels were documented before and after therapy. Dosimetry was performed in 30 patients.

Results: ^{177}Lu-PSMA demonstrated high absorbed tumor doses (median, 3.3 mGy/MBq) as compared to normal organs. Parotid glands received higher doses (1.3 mGy/MBq) than kidneys (0.8 mGy/MBq). All patients tolerated the therapy without any acute adverse effects. Except mild reversible xerostomia in two patients, no long-term side effect was observed. There was a small, but statistically significant reduction in erythrocyte and leukocyte counts, of which only the erythrocytes decreased slightly below the normal range. No thrombocytopenia occurred. The severity of pain significantly reduced in 2/6 (33.33%) patients. Decrease in PSA was noted in 45/56 (80.3%) patients. In 25 patients, followed up at least 6 months after ≥2 PSMA-RLT cycles, molecular response evaluation (^{68}Ga-PSMA PET/CT) revealed partial remission (PR) in 14, stable disease (SD) in 2 and progressive disease (PD) in 9 patients. Contrast-enhanced CT exhibited PR in 5, SD in 13, and PD in 7 patients. The median

progression-free survival was 13.7 months, and the median overall survival was not reached at follow-up of 28 months.

Conclusions: PSMA-RLT with ^{177}Lu-PSMA is feasible, safe and effective in end-stage progressive mCRPC with appropriate selection and follow-up of patients by ^{68}Ga-PSMA PET/CT applying the concept of Theranostics.

Keywords: PSMA, Radioligand Therapy, Theranostics

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) has a poor prognosis with estimated 27,540 prostate cancer deaths in the US in 2015 *(1)*. The novel agents abiraterone and enzalutamide provide limited survival benefit of 3.9 and 4.8 months, respectively *(2,3)*. Overall survival has been reported to improve with ^{223}Ra-chloride by 3.6 months, but it is indicated for patients with skeletal metastases *(4)*. Immunotherapy with Sipuleucel-T confers survival benefit of a few months, but has no impact on the time-to-progression, and is associated with immunological adverse events *(5)*.

Prostate specific membrane antigen (PSMA) is a glutamate carboxypeptidase II (GCPII), over-expressed in prostate cancer *(6)*. Pomper et al. in 2002 performed the first in-vivo study using a urea-based compound targeting PSMA for diagnosis *(6)*. Their high-affinity urea-based inhibitor of PSMA maintained target specificity after radiolabeling with ^{68}Ga *(7)*. ^{68}Ga-labeled PSMA inhibitors with HBED-CC as chelator (^{68}Ga-PSMA-HBED-CC) have been successfully used for the imaging of prostate cancer with high sensitivity and specificity *(8,9)*. These small molecules penetrate solid tumors and have the advantage of rapid clearance from blood as compared to whole antibodies.

Radioimmunotherapy using PSMA antibody ^{177}Lu-DOTA-J591 was limited by myelosuppression and non-hematological toxicity, with a maximum tolerated activity per cycle of 2,450 MBq/m^2 *(10)*.

Zeichmann et al. performed endoradiotherapy of mCRPC using a PSMA small molecule labeled with ^{131}I *(11)*. The ^{68}Ga-/^{111}In-/^{177}Lu-labeled diagnostic or therapeutic

PSMA-ligand (DOTAGA-(I-y)fk(Sub-KuE), also named PSMA-I&T for 'imaging and therapy', possesses a unique potential for the management of advanced prostate cancer *(12-14)*. PSMA radioligand therapy (RLT) using PSMA-I&T could achieve high tumor-to-background ratios of the mean absorbed doses *(13,15)*.

We analyzed the safety and efficacy of ^{177}Lu-labeled DOTAGA-based PSMA ligand ^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE) (^{177}Lu-PSMA) for the first time in a larger cohort of patients with mCRPC. The end points of our analysis, which was performed in correlation with kinetics and dosimetry, were safety, objective response, progression-free survival and overall survival.

MATERIALS AND METHODS

Patient characteristics

Fifty-six patients with progressive mCRPC (median age 72y, median Gleason score 8), referred to our center with rising prostate specific antigen (PSA), underwent 125 cycles of ^{177}Lu-PSMA RLT between May 2013 and June 2015 (number of cycles – 1: n=10, 2: n=15, 3: n=17, 4: n=6, 5: n=2). The median administered activity of ^{177}Lu-PSMA per cycle was 5.76 GBq (range 3.6 – 8.7 GBq). The patients were clinically followed up according to Karnofsky performance score (KPS), visual analog scale (VAS) for pain, and for any other clinical symptoms as documented on patient questionnaires (Tables 1 and 2). The institutional review board approved this study and all patients signed a written informed consent.

Selection of patients and follow-up

PSMA expression was an essential prerequisite for ^{177}Lu-PSMA RLT. To avoid the introduction of two new radiopharmaceuticals for imaging and therapy in one study, ^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA) was used instead of the corresponding ^{68}Ga-DOTAGA-(I-y)fk(Sub-KuE) for selection of patients and therapy monitoring by means of PET/CT. The administered activity of ^{177}Lu-PSMA, number and interval of cycles were personalized, based on the uptake in metastases on pre-therapy ^{68}Ga-PSMA PET/CT, renal function, hematological status, previous treatments and KPS. Molecular and morphological response was evaluated according to the EORTC criteria *(16)* and RECIST 1.1 *(17)*, respectively. Serum PSA response was documented monthly. At the time of analysis, follow-up for median 15 months (range 6-28 months) after ≥2 therapy cycles was available in 25 patients (2 cycles: n=8; 3 cycles: n=6; 4 cycles: n=9).

Ethical and regulatory issues

^{68}Ga- and ^{177}Lu-PSMA were administered in compliance with the German Medicinal Products Act, AMG (§13, 2b), the 1964 Helsinki declaration, and the responsible regulatory body (Government of Thuringia). All patients received PSMA-RLT under the 'compassionate use' clause of the AMG *(18)*. The decision to perform PSMA-RLT was based on the opinion of the referring urologists and oncologists after exhaustion of all other therapeutic options. The study was performed according to the regulations of the German Federal Agency for Radiation Protection.

Gallium-68 PSMA-HBED-CC PET/CT imaging

PET/CT (Biograph mCT Flow 64; Siemens Medical Solutions AG, Erlangen, Germany) was performed 60-80 min after i.v. administration of 142±18 MBq ^{68}Ga-PSMA. All patients received 20 mg of furosemide i.v. to accelerate renal tracer excretion. Spiral contrast-enhanced CT (ceCT) was acquired after intravenous administration of 60-100 mL nonionic iodinated contrast. Imaging/reconstruction parameters were: 120 kV, 160 mA, gantry rotation time 0.3s, slice thickness 0.4mm with increment of 0.1-10 mm, 40 images/second, 512x512 matrix. PET imaging was acquired from the skull through mid-thigh in 3D flow motion. Reconstruction matrix was 400x400 (Hi-REZ processing), achieving an axial resolution of 4.4 mm. Maximum standardized uptake values (SUV_{max}) were obtained by drawing circular regions of interest, which were automatically adapted (40% isocontour) to a 3D volume of interest using commercial software provided by the vendor.

Lutetium-177 radiolabeling

^{177}Lu-labeling of the DOTAGA-based PSMA ligand (DOTAGA-(I-y)fk(Sub-KuE) was performed using previous published methods *(12)*. In brief, the PSMA ligand was incubated with the required radioactivity of ^{177}Lu-Cl_3 at 90 °C for 30 min in sodium acetate buffer (0.4 M, pH 5.5). To this buffer, 5-10 mg of gentisic acid was added to prevent radiolysis. After sterile filtration and quality control, the radiochemical purity was more than 97% in all cases, mostly >99%.

Hydration and administration of therapeutic activity

Each patient received 1.6L of 5% lysine HCl and 10% L-arginine HCl amino acid solution intravenously over 4 hours, starting 30 minutes prior to the radiopharmaceutical *(19)*. The radiopharmaceutical was co-administered over 10-15 minutes using a dedicated second infusion pump system for radionuclide therapy.

Safety

All patients were clinically monitored for the therapy and 2–4 days thereafter as in-patient, for possible side effects (nausea, vomiting, breathlessness, fatigue, etc.). Vital parameters were recorded during therapy. A structured questionnaire was used to document any delayed complication (e.g. xerostomia). Laboratory analysis was performed pre- and post-PSMA-RLT (Table 3). Toxicity was recorded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 *(20).*

Dosimetry

Dosimetry was performed in 30 patients according to our established protocol in over 1,000 neuroendocrine neoplasm patients undergoing peptide receptor radionuclide therapy *(21)*. Time-dependent activity in organs and tumors was determined by drawing regions of interest on serial ^{177}Lu-PSMA whole-body post-therapy scans. The time-activity curves of source regions were fitted to exponential functions of first or second order to determine the time-integrated activity. The mean absorbed doses were estimated using OLINDA/EXM software *(22)*.

Blood sampling was performed in six patients to estimate the mean absorbed dose to red marrow (RM). Venous blood samples were obtained at different time points post injection (p.i.) of radiopharmaceutical. The radioactivity was measured using a high-purity germanium detector (MBq/mL) and was plotted against time. The curves were fitted to bi- or tri-exponential functions to determine the radioactivity in blood. Cumulative radioactivity in bone marrow was calculated as described previously *(23)*.

Post-therapy whole-body scintigraphy was performed using MEDISO spirit DH-V dual-headed gamma camera (Medical Imaging Systems, Budapest, Hungary) with MeGP collimator, 15% energy window, peak at 208 keV, scan speed 15 cm/min. Whole-body scintigraphy was acquired at 5 time points from 0.5 h to 118 h p.i. SPECT/CT was obtained between 45 h and 118 h p.i.

Statistics

Statistical analysis was performed using ORIGINPRO 8.1G software. After proving the skewed distribution of all variables using the Kolmogorov–Smirnov test, quantitative data were described in terms of median and range. Non-parametric sign tests were used for the determination of significance of difference between hematological and renal parameters pre- and post-therapy; *P*-values ≤0.05 were considered significant. Survival analysis was performed using Kaplan-Meier curves.

RESULTS

^{177}Lu-PSMA post-therapy scintigraphy

Excellent uptake of ^{177}Lu-PSMA was noted in the metastases and in residual or recurrent prostate cancer (n=10) on post-therapy planar and SPECT/CT images (Figs. 1 and 2). Physiological uptake was seen in lacrimal and salivary glands, small intestine, kidneys, and a relatively less uptake in the liver and spleen. The radiopharmaceutical was predominantly excreted via the kidneys. No uptake was seen in the lungs or the brain. Delayed whole-body images (up to 118 hours post-therapy) exhibited long-term retention of ^{177}Lu-PSMA in the metastases with relative rapid clearance from normal organs.

Dosimetry

Blood sampling revealed fast kinetics of ^{177}Lu-PSMA, especially for first of the three exponential functions. The mean absorbed dose to the RM in six patients varied from 0.01 – 0.04 mGy/MBq (Table 4). The effective half-life in tumor lesions was higher than in whole body, kidneys and parotid glands, resulting in higher mean absorbed doses delivered to the tumors (Fig. 3; Table 5). The maximum absorbed dose delivered to a para-aortic lymph node metastasis, which exhibited the highest SUV_{max} (187.5) before therapy, was 468 Gy.

Safety

^{177}Lu-PSMA therapy was well-tolerated by all patients. No clinically significant adverse effects were reported by any patient during hospitalization for therapy and on follow-up of 28 months. Two patients reported mild xerostomia after receiving 3 and 4 cycles, respectively, with spontaneous resolution within 3 months.

No significant change in hemoglobin (median ± SD; pre-therapy 7.8±1.1 mmol/l, post-therapy 7.7±1.2 mmol/l, *p>0.05*) was observed after therapy (Fig. 4). Three anemic patients required packed red cell transfusions prior to PSMA-RLT. There was a statistically significant decrease in the erythrocyte counts (pre-therapy 4.3±0.6, post-therapy 4.0±0.5; *p<0.05*) and leukocyte counts (from 6.1±1.4 to 5.6±1.6; *p<0.05*), although the absolute difference was minimal and clinically insignificant. Platelets remained within the normal range (pre-therapy 219±51, post-therapy 207±49, *p>0.05*). Grade 1-2 leukocytopenia occurred in 9 patients, who had received long-term chemotherapy. Remarkably, patients with low blood counts before therapy did not exhibit a decrease of blood cell counts after ^{177}Lu-PSMA therapy (Table 6).

There was no evidence of nephrotoxicity (Fig. 4). One patient with previous grade 1 renal insufficiency did not experience worsening of renal function. There was no statistically significant change in serum creatinine (pre-therapy 81.9±22.4 mmol/l, post-therapy 80.9±23.7 mmol/l; *p>0.05*).

Efficacy of ^{177}Lu-PSMA-RLT

Improvement of clinical symptoms. Pain significantly decreased in severity in 2/6 (33.33%) patients, with a reduction in VAS from 8 to 4 and from 6 to 3 pre- and post-PSMA-RLT, respectively. The pain intensity remained unchanged in 4 patients, requiring constant use of analgesics. KPS improved in several patients and no worsening was observed in any patient after therapy.

PSA response. Out of 56 patients, 45 (80.3%) demonstrated reduction in PSA levels (Fig. 5). The median PSA at first presentation was 43.2 ng/mL (0.05 – 2848 ng/mL) and

decreased to 23.8 ng/mL (0.01 – 2227 ng/mL) after therapy. A decline in PSA by >80% was seen in 13 (23.2%), by >50% in 33 (58.9%), and by >30% in 37 (66.1%) patients. Best PSA response was a decline from 29.12 to 0.23 ng/mL (99.2%) post-therapy. A PSA increment of >25% was noted in 6 (12.8%) patients with progressive disease *(24)*.

Objective response. Analysis was performed in 25 patients followed up at least 6 months after two or more ^{177}Lu-PSMA RLT cycles (Fig. 5).

Morphological response assessment (RECIST 1.1) by ceCT documented PR in 5 (20%), SD in 13 (52%) and PD in 7 (28%) patients. In patients exhibiting objective response, 4 had lymph node metastases only, and one patient had multiple lymph node and bone metastases, with only the target lymph node lesion demonstrating a significant decrease in size (Figs. 1 and 6).

On ^{68}Ga-PSMA PET/CT (EORTC criteria), the median SUV_{max} of the target lesion before therapy was 37.5 (range 15 – 187.5), and post PSMA-RLT was 15.7 (1.7 – 75.3). Molecular response evaluation revealed PR in 14 (56%), SD in 2 (8%) and PD in 9 patients (36%). Objective responses were also observed in 9 patients with either only or predominantly bone metastases. There was a 90% reduction in SUV_{max} (from 187.5 to 15.9) of the para-aortic lymph node metastasis receiving 468 Gy absorbed dose.

Survival

Over a follow-up period of 28 months, 12 (21.4%) patients died. The median OS (last assessed 15.5 months post-PSMA-RLT) has not yet been reached (Fig. 7A). Survival

after 28 months is 78.6%. The median progression-free survival was 13.7 months (Fig. 7B).

DISCUSSION

Lutetium-177 PSMA-RLT involves selective tumor targeting with the objective of maximizing tumor dose and sparing normal tissue. ^{177}Lu-PSMA showed high, specific and rapid uptake in prostate cancer metastases. The long effective half-life in both, skeletal and soft tissue metastases, approaching the physical half-life of ^{177}Lu, resulted in a high mean absorbed tumor dose with a maximum of 260 Gy and 468 Gy obtained in bone and lymph node metastases, respectively. Our patient group was heterogeneous with wide variation in the pre-PSMA-RLT SUV_{max}, in tumor load and distribution of metastases (Table 2). The excellent tumor response is attributable to the high doses delivered to metastases based on the specific ^{177}Lu-PSMA tumor uptake *(25,26)*.

PSMA-RLT has a distinct advantage over radioimmunotherapy utilizing ^{177}Lu-labeled PSMA antibodies. Mean absorbed doses in mGy/MBq by ^{177}Lu-PSMA delivered to whole-body, red marrow and kidneys (median 0.02, 0.014, and 0.8, respectively) were found to be significantly lower than those by ^{177}Lu-DOTA-J591 (mean 0.19, 0.32, and 1.40, respectively) *(10)*. The larger size of the antibodies results in slower clearance from circulation, thereby delivering much higher doses to normal organs. The mean absorbed dose to RM by ^{177}Lu-DOTA-J591 was 20-fold higher when compared to ^{177}Lu-PSMA in this study *(10)*.

Theranostics encompasses the use of molecular targeting vectors (e.g. peptides, ligands etc.), which can be labeled with distinct radionuclides for diagnosis and therapy *(27)*. In this study, the essential selection criterion was the confirmation of PSMA expression of the metastases on ^{68}Ga-PSMA PET/CT. This theranostic approach also aids in the early and accurate assessment of therapy response *(28)*. The disease burden can be accurately quantified by SUVs using ^{68}Ga-PSMA PET/CT, making follow-up easy in mCRPC patients undergoing PSMA-RLT.

For the first time, in our study, objective response evaluation after radiolabeled PSMA small molecule therapy has been systematically performed. Significant reduction in size of the target lesion was noted in 5 patients with lymph node metastases. The discrepancy in the evaluation of remission in 9 patients, classified as responders by PET/CT, can be explained by the lower sensitivity of stand-alone CT in the assessment of skeletal lesions.

Based on pre- and post-therapeutic SUV of the target lesions, the disease progressed after 2 cycles in 9 patients presenting with extensive lymph node and osseous metastases. The discordance in 2 patients with extensive disease, demonstrating PD on ^{68}Ga-PSMA PET/CT and SD on CT, can be explained by the higher sensitivity of PET/CT (particularly for small lymph node lesions), and that molecular response (as defined by SUV-change) occurs earlier than change in size *(28,29)*.

There was a decrease in serum PSA in 45/56 (80.3%) patients, and by >50% in 33 (58.9%) patients, similar to the results reported earlier *(11)*. The major route of excretion

of ^{177}Lu-PSMA is through kidneys, similar to ^{177}Lu-DOTATATE *(19)*. The high renal uptake may be due to PSMA expression in renal tissue, which was better visualized on the early ^{177}Lu-PSMA post-therapy images *(30)*. Blocking of specific PSMA-binding in the kidney tissue by the PSMA-inhibitor 2-(phosphonomethyl)pentanedioic acid (PMPA) has been validated in pre-clinical studies; but there is a lack of availability of this compound for clinical use, and its use may concurrently block uptake within tumor *(31)*. The patients were hydrated using a combination of positively-charged amino acids, as for PRRT using somatostatin analogs. There was no evidence of nephrotoxicity after PSMA-RLT. However, the role of nephroprotection needs to be further investigated. The rapid washout of ^{177}Lu-PSMA resulted in relatively low mean absorbed dose despite the high initial renal uptake. Dosimetry ensured that the maximal mean absorbed renal dose of 23 Gy, extrapolated from external beam radiotherapy, was not exceeded *(32)*.

A higher incidence of hematotoxicity (40%) was reported in a smaller study of 10 patients treated with ^{177}Lu-DKFZ-617, with one patient suffering grade 3–4 hematological toxicity *(33)*. This could be explained by a more compromised bone marrow of these patients before PSMA-RLT. Grade 1–3 hematological toxicity was reported with ^{131}I-labeled PSMA ligands, *(11)*. There was a mild but statistically significant decrease in mean leukocyte counts in our patient cohort. However, 17 patients presented with pre-existing grade 1-2 anemia and leukocytopenia before PSMA-RLT, without worsening of blood counts after therapy (Table 6). Leukocytopenia of grade 1-2 was present in 9/25 (36%) patients who had already received chemotherapy before PSMA-RLT. No thrombocytopenia occurred. There was no grade 3 or 4 hematological toxicity in any of the patients, despite the high administered

radioactivity up to 8.7 GBq.

The uptake in salivary glands and in the proximal small intestine can be explained by PSMA expression *(30)*. Mean absorbed dose to the parotids was found to be greater than that to the kidneys. This was also observed in a recent preclinical dosimetry study of ^{177}Lu-DKFZ-617 *(34)*. None of our patients experienced significant xerostomia. Intense accumulation of ^{131}I-MIP-1095 in the salivary glands reportedly led to xerostomia in 7 patients and mucositis in 1 patient *(11)*. The high dose delivered to salivary glands by ^{131}I-MIP-1095 was probably due to the prolonged retention. Since ^{177}Lu-PSMA, in contrast to ^{131}I-MIP-1095, did not give rise to salivary toxicity, different fate of the labels over time are assumed in salivary glands and should be investigated. No short or long-term side effects from the therapy (nausea, vomiting, diarrhea, etc.) were observed in any patient despite accumulation of the radiopharmaceutical in the small bowel and significant elimination of activity by the intestine.

Morphological response was better appreciated in lymph node metastases as compared to bone lesions, primarily due to better delineation of lymph nodes on CT. A significant advantage of ^{177}Lu-PSMA over bone-targeting radiopharmaceuticals, notably ^{223}Ra-chloride, is the utility in mCRPC with not only osseous, but also soft tissue metastases. It should be emphasized that 12 of our patients presented with lymph node metastases only, and 8 of them responded to PSMA-RLT not only according to molecular, morphological and biochemical (PSA-reduction) criteria, but also clinically, as noted by a significant decrease in inguinal pain in 1 patient. Further clinical trials comparing ^{177}Lu-PSMA and ^{223}Ra-chloride are needed in patients with skeletal

metastases, with regard to objective response, pain management, as well as adverse effects on the bone marrow.

Objective responses to ^{177}Lu-PSMA were noted even in patients having relapsed under maximum hormonal therapy. There is no existing evidence to suggest whether hormonal agents affect PSMA expression on metastases. Therefore, we postulate that these drugs should not be stopped during or after PSMA-RLT.

Our single-center prospective clinical study had some limitations. There were no strict pretest criteria for selection of patients and they comprised a very heterogeneous group. However, PSMA-RLT was a rational therapeutic option applying a systematic individualized theranostic approach comprising of ^{68}Ga-PSMA PET/CT for selection of patients, ^{177}Lu-PSMA based therapy, and ^{68}Ga-PSMA PET/CT based response evaluation. The decision to treat was taken by the referring oncologists and urologists after exhaustion of all standard therapeutic options. Median progression-free survival (13.7 months) obtained in our study is at least comparable to newer therapies for mCRPC *(2-5)*. Progression-free survival was retained in many patients despite having received the currently available therapy options, including chemotherapy, which potentially limited the amount of radioactivity that could be applied for PSMA-RLT.

CONCLUSION

Lutetium-177 PSMA radioligand therapy in end-stage progressive mCRPC is safe and effective. The avidity of the tumor target that defines the achievable tumor dose was demonstrated prior to therapy using ^{68}Ga-PSMA PET/CT, utilizing theranostic approach. PET/CT was applied for monitoring tumor response and to decide on further

personalized treatment. This novel therapy achieves objective responses in patients who have progressed on all standard treatments for prostate cancer with minimal toxicity.

DISCLOSURE

Hans-Jürgen Wester is a shareholder of Scintomics, GERMANY. Other authors have nothing to disclose.

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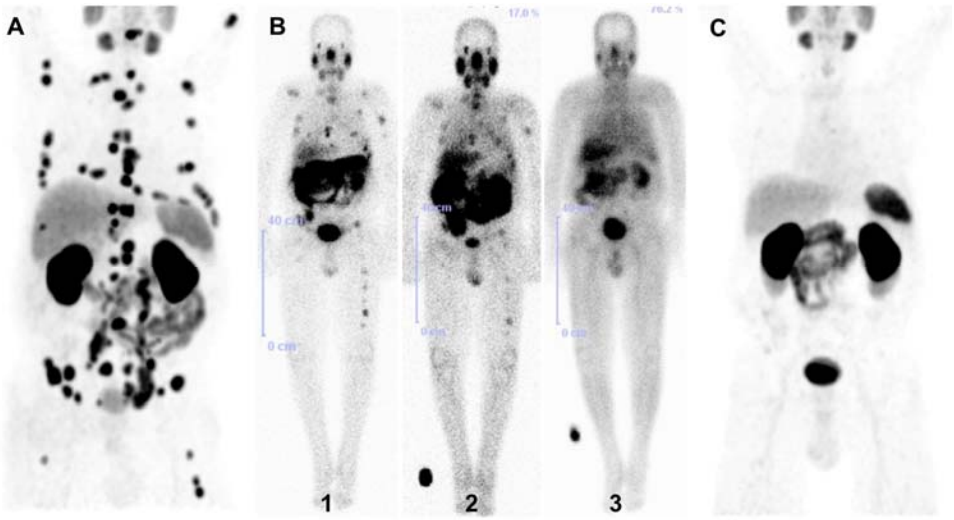

FIGURE 1: 76-year-old patient post-EBRT to bone metastases and hormone therapy, showed progressive bone and lymph node metastases on ^{68}Ga-PSMA PET/CT *(A)*. ^{177}Lu-PSMA scintigraphy following 1st, 2nd and 3rd RLT cycles, respectively; demonstrate resolution of metastases *(B – 1, 2, 3)*. ^{68}Ga-PSMA PET/CT after 3 PSMA-RLT cycles demonstrates excellent molecular response (RECIST 1.1 and EORTC criteria) with disappearance of most of the PSMA-avid metastases *(C)*.

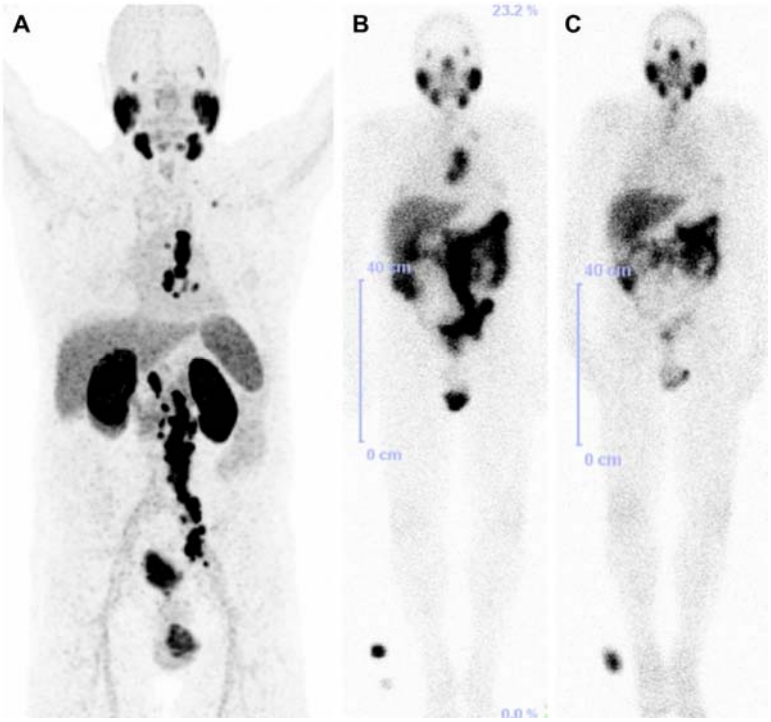

FIGURE 2: 70-year-old patient with PSMA-avid lymph-node metastases on pre-therapy ^{68}Ga-PSMA PET/CT *(A)*, and on ^{177}Lu-PSMA scintigraphy after 1st PSMA-RLT *(B)*; with remarkable reduction of uptake after 2nd PSMA-RLT *(C)*, consistent with excellent therapy response.

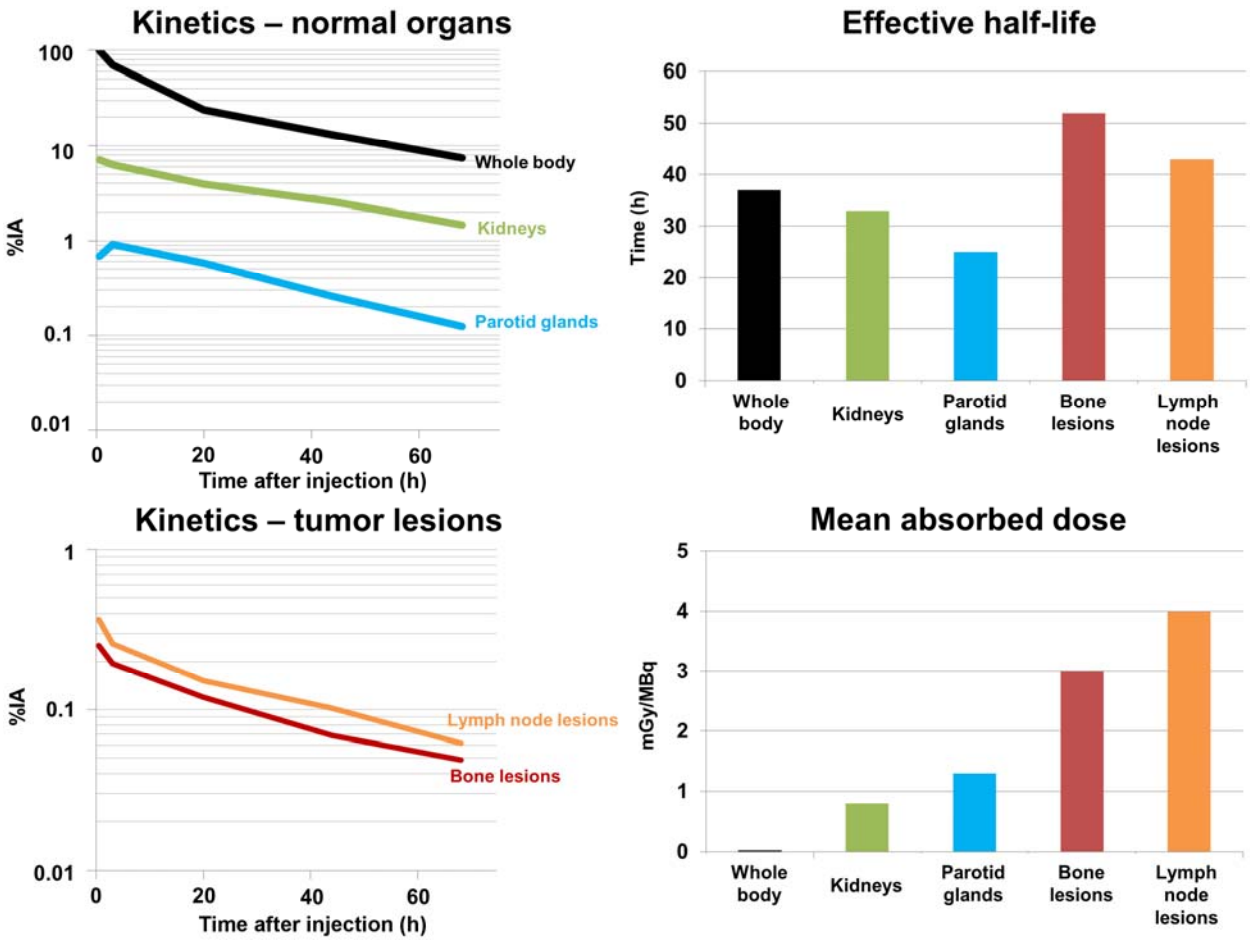

FIGURE 3: Kinetics, effective half life and mean absorbed doses (median) in normal organs and tumor lesions

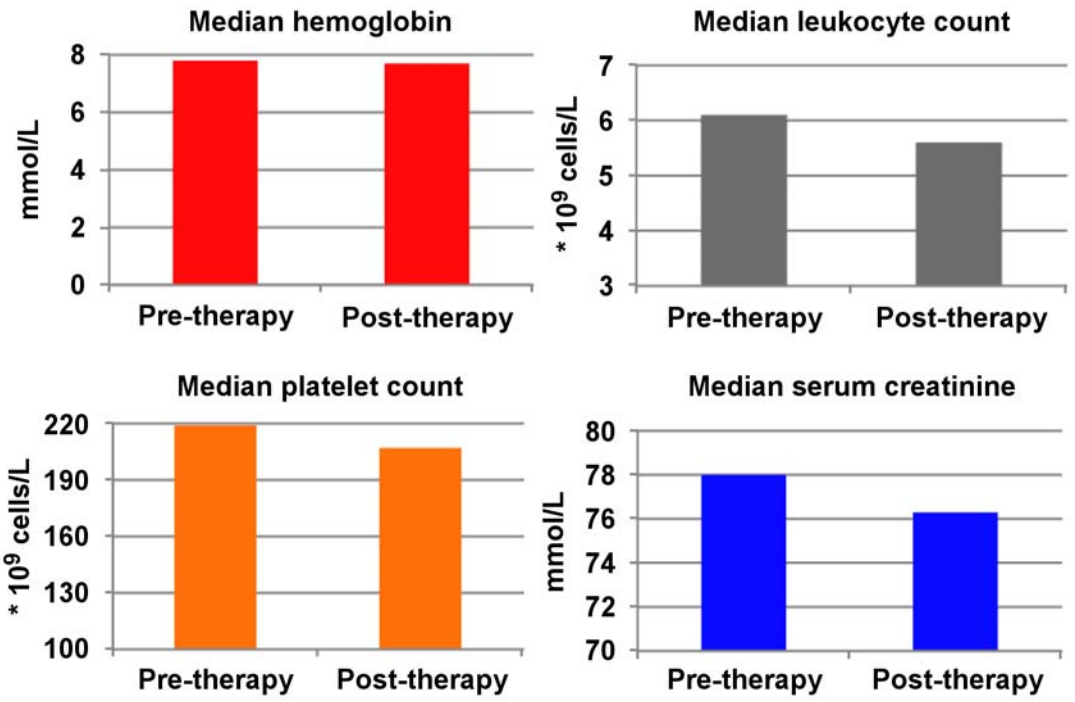

FIGURE 4: Comparison between the median pre- and post-PSMA-RLT laboratory parameters demonstrating no significant hematotoxicity or nephrotoxicity

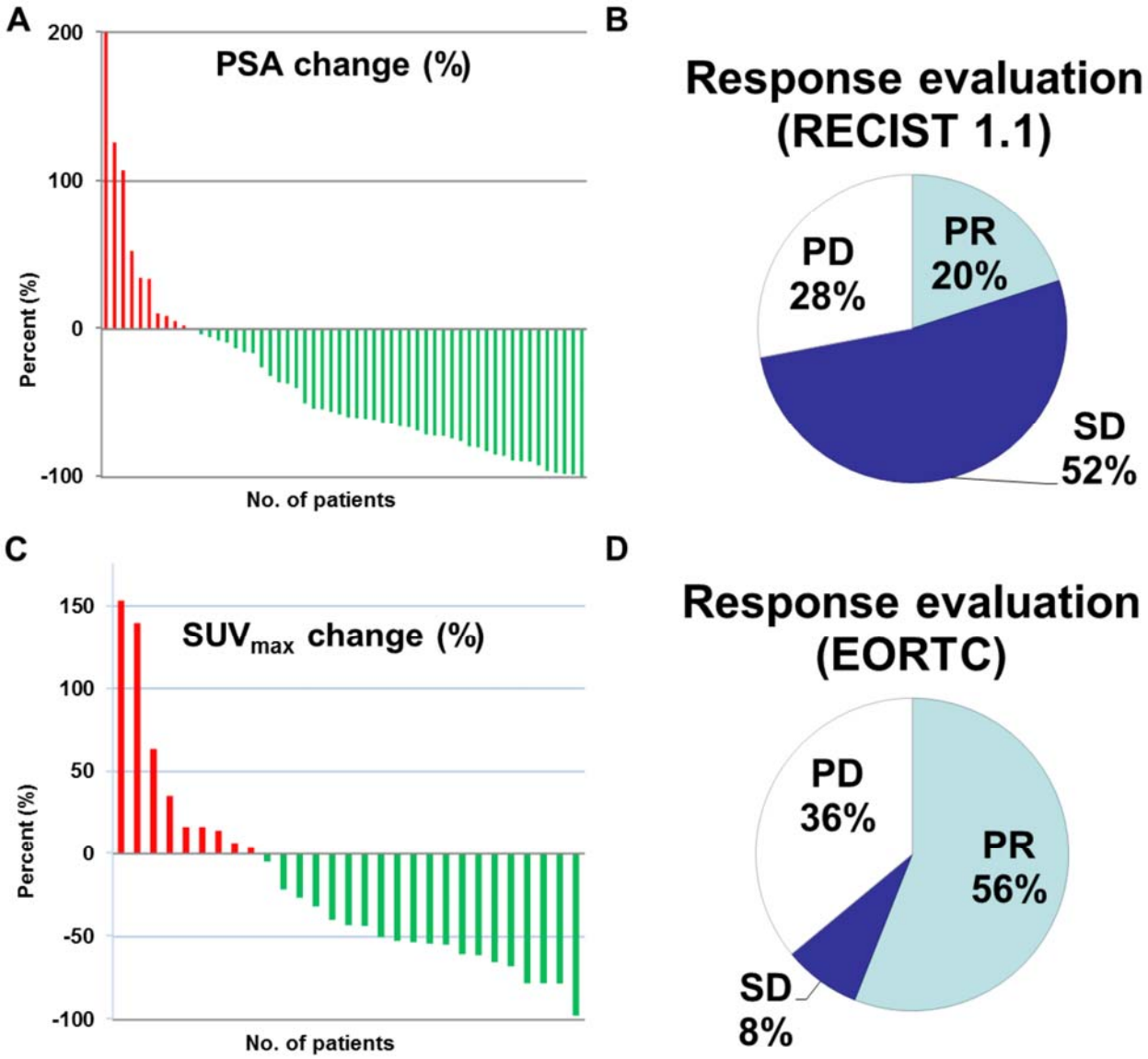

FIGURE 5: Percentage (%) change in baseline serum PSA (*A*) and in baseline SUV_{max} over the time of follow-up (*B*). Response assessment in 25 patients after ≥2 PSMA-RLT-cycles: RECIST 1.1 *(C)* and EORTC criteria *(D)*

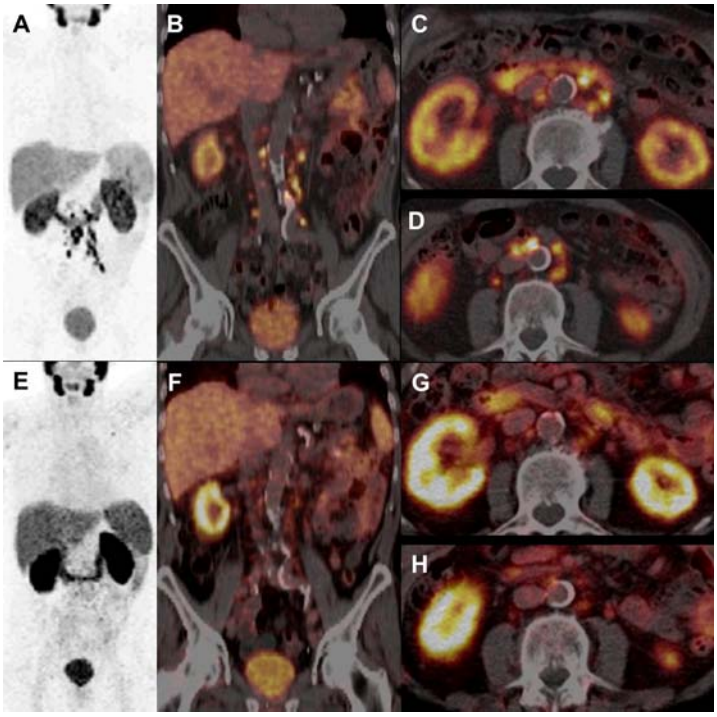

FIGURE 6: 75-year-old patient after prostatectomy, EBRT to bone metastasis, hormone therapy, and chemotherapy, was referred with multiple PSMA-avid lymph node metastases (^{68}Ga-PSMA PET/CT, *A*-*D*). An excellent response to therapy (both according to RECIST 1.1 and EORTC criteria) was observed after 2-cycles of ^{177}Lu-PSMA RLT on ^{68}Ga-PSMA PET/CT *(E- H)*, with >50% decrease in serum PSA level (from 15 to 6 ng/ml).

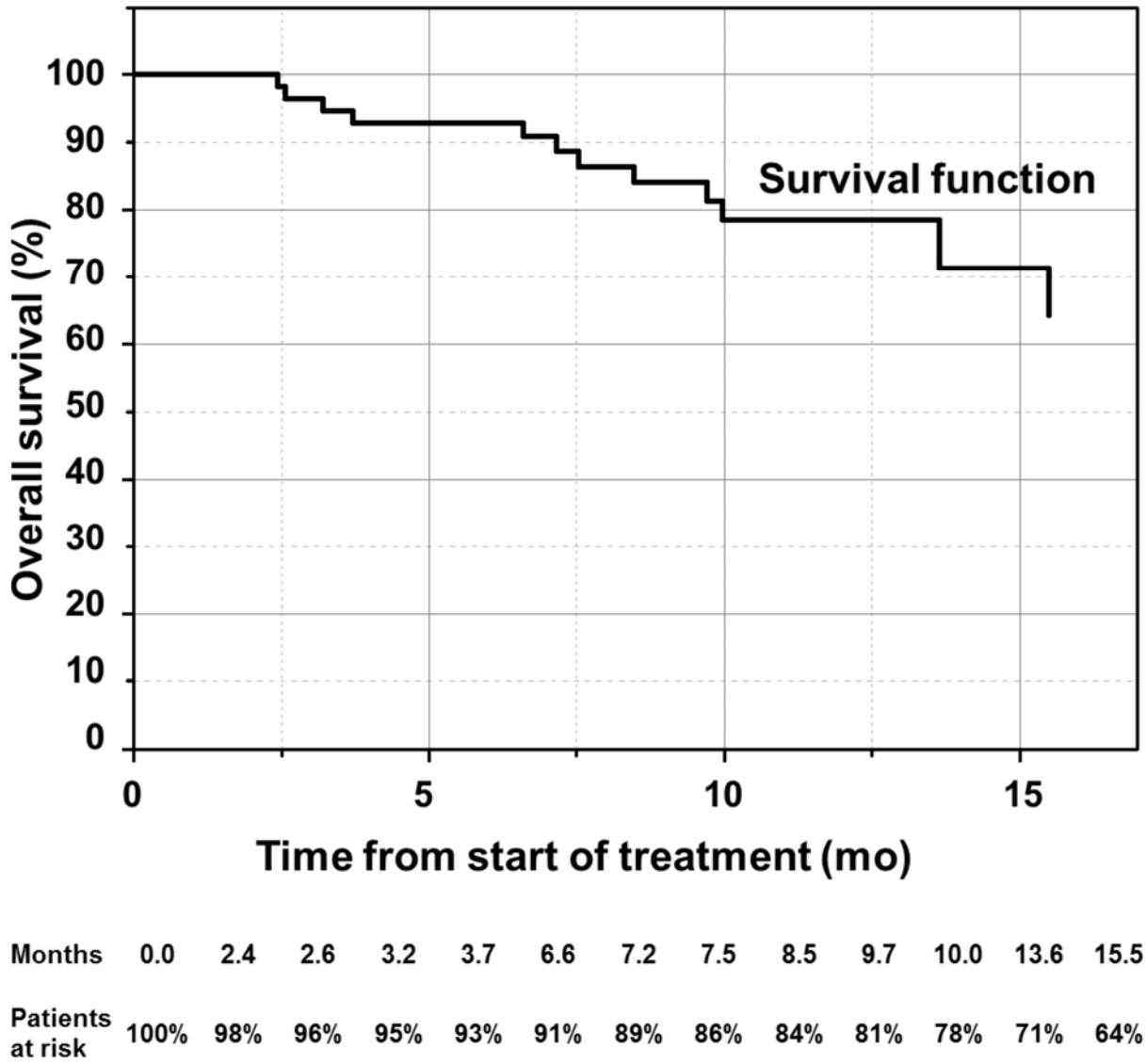

FIGURE 7A: Survival function: overall survival (months)

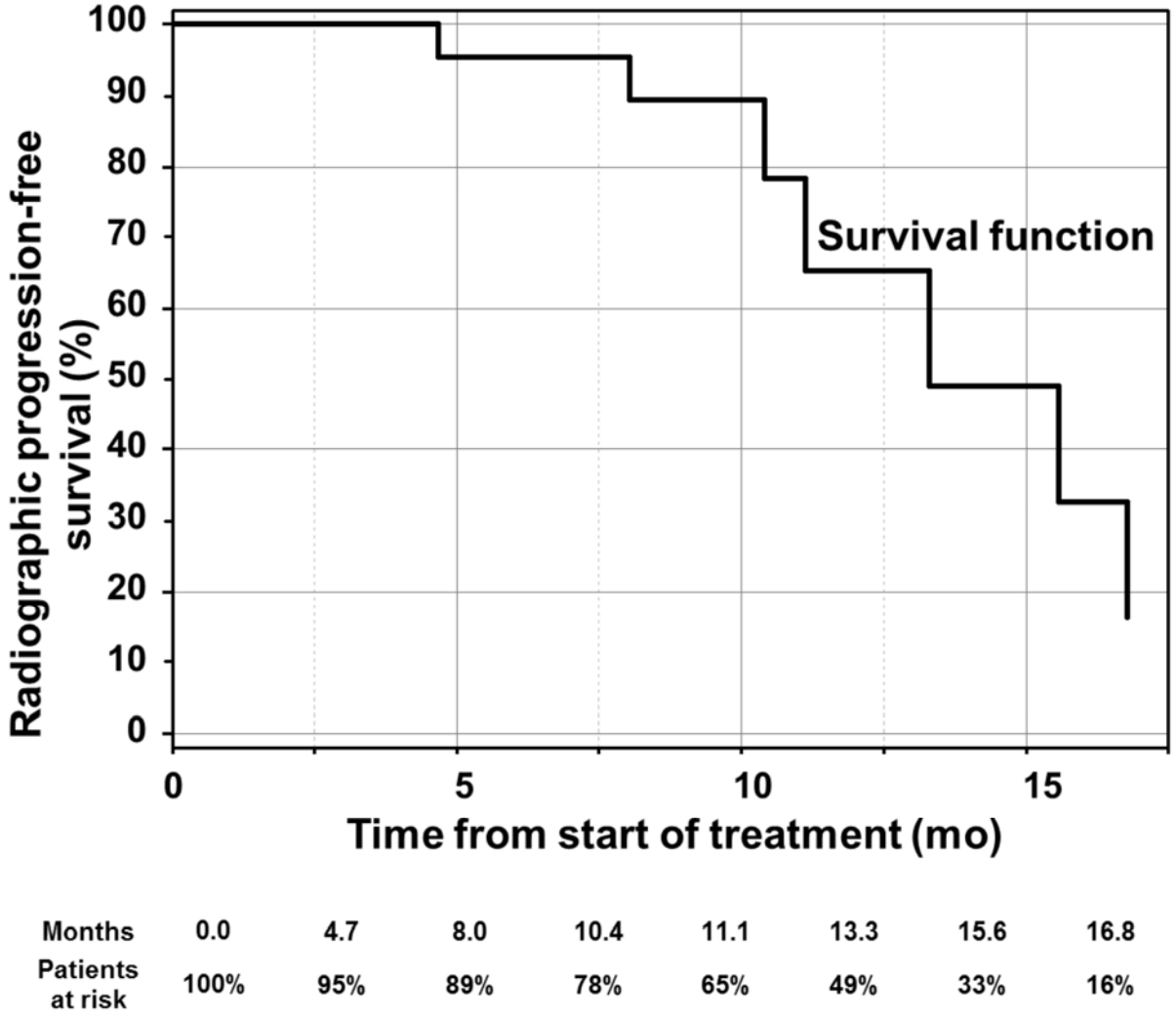

FIGURE 7B: Survival function: progression-free survival (months) according to RECIST 1.1

Characteristic	Sub-group	Median	Range	No. of patients
Age at first PSMA-RLT (years)	overall	72	50 – 88	
Time interval: diagnosis to first PSMA-RLT (years)	overall	7.5	2.5 – 14	
Follow-up after final PSMA-RLT (months)	overall	15	6 – 28	
Karnofsky Performance Score (KPS %)	overall	80	70 – 90	
	KPS 70%			23
	KPS 80%			14
	KPS 90%			19
Pain (VAS)	overall			6
	VAS < 6			4
	VAS ≥ 6			2
Tumor stage	pT1			1
	pT2			13
	pT3			35
	pT4			7
Previous therapies	Prostatectomy			40
	EBRT			47
	Chemotherapy			25
	Ra-223 Chloride			1
	Hormone therapy			56
	LHRH analogs			56
	Cyproterone			17
	Bicalutamide			26
	Abiraterone			21
	Enzalutamide			11

TABLE 1: Patient characteristics

Tissue / Organ	No. of patients
Skeletal	43
Lymph node	44
Liver	5
Lung	7
Other metastases	3
Brain	1
Pleuroperitoneal	1
Testicular and adrenal	1

TABLE 2: Localization of metastases

Category	Specific test
Full blood count	Hemoglobin, erythrocytes, leukocytes, platelets, red and white cell differential counts
Electrolytes	K^+, Na^+, Ca^{++}, Cl^-
Renal profile	Urea, creatinine, eGFR
Liver panel	Total bilirubin, liver enzymes, albumin, globulin
Coagulation profile	PT, INR, aPTT
Glycemic profile	HbA1c, random blood glucose
Thyroid function	TSH
Acute-phase proteins	CRP, Ferritin
Urine examination	Routine urine analysis

TABLE 3: Laboratory parameters followed up after PSMA-RLT

Patient	$T_{½,1}$ (h)	$T_{½,2}$ (h)	$T_{½,3}$ (h)	Mean absorbed dose to red marrow (mGy/MBq)
P1	0.3	3	94	0.01
P2	0.3	4	29	0.02
P3	0.2	3	30	0.03
P5	0.1	1	9	0.03
P6	0.2	2	42	0.02
P8	0.2	2	11	0.04

TABLE 4: Blood kinetics and absorbed dose to red marrow in 6 patients ($T_{½,1/2/3}$: half-life of the first, second and third exponential functions, respectively)

	Effective half-life (h)				Mean absorbed dose (mGy/MBq)				Median dose (mGy) per ^{177}Lu-PSMA-RLT cycle (6000 MBq)
	min	**max**	**median**	**SD**	**min**	**max**	**median**	**SD**	
Whole body	21	91	37	19	0.01	0.07	0.02	0.01	120
Kidneys	19	83	33	14	0.2	1.9	0.8	0.4	4800
Parotid glands	20	43	25	5	0.3	9.5	1.3	2.3	7800
Tumor lesions (all)	14	160	51	30	0.03	78	3.3	14	19800
Bone metastases	14	149	52	30	0.2	40	3.0	10	18000
Lymph node metastases	25	160	43	32	0.14	78	4.0	20	24000

TABLE 5: Effective half-life and mean absorbed doses in whole body, kidneys, parotid glands and tumor lesions

Hematotoxicity according to CTCAEv4.03

Grade	Anemia		Leukocytopenia		Thrombocytopenia	
	Pre-PSMA-RLT	Post-PSMA-RLT	Pre-PSMA-RLT	Post-PSMA-RLT	Pre-PSMA-RLT	Post-PSMA-RLT
G1	14	14	4	4	0	0
G2	3	3	5	5	0	0
G3	0	0	0	0	0	0
G4	0	0	0	0	0	0
G5	NA	0	NA	0	NA	0

NA: Not applicable pre-PSMA-RLT (G5 represents death)

TABLE 6: No evidence of hematotoxicity following PSMA-RLT