Prostate-specific membrane antigen radioligand therapy using $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: comparison of safety, biodistribution and dosimetry

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ABSTRACT

The objective of this study was to determine the safety, kinetics and dosimetry of \(^{177}\)Lu labeled prostate specific membrane antigen (PSMA) small molecules \(^{177}\)Lu-PSMA-I&T and \(^{177}\)Lu-PSMA-617 in a large cohort of patients with metastatic castration-resistant prostate cancer (mCRPC) undergoing PSMA radioligand therapy (PRLT). **Methods:** A total of 138 patients (mean age, 70±9 y; age range 46-90 y) with progressive mCRPC and PSMA expression verified by \(^{68}\)Ga-PSMA-11 PET/CT underwent PRLT. 51 patients received 6.1±1.0 GBq (range, 3.4-7.6 GBq) \(^{177}\)Lu-PSMA I&T and 87 patients received 6.5±1.1 GBq (range, 3.5-9.0 GBq) \(^{177}\)Lu-PSMA-617. Dosimetry was performed in all patients on the identical protocol. The mean absorbed doses were estimated with OLINDA software (MIRD Scheme). Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. **Results:** The whole-body half-lives were shorter for \(^{177}\)Lu PSMA I&T (35 h) as compared to \(^{177}\)Lu PSMA-617 (42 h). The mean whole-body dose of \(^{177}\)Lu-PSMA-617 was higher as compared to \(^{177}\)Lu-PSMA-I&T (0.04 Gy/GBq vs. 0.03 Gy/GBq, p<0.00001). Despite the longer half-life of \(^{177}\)Lu-PSMA-617, the renal dose of \(^{177}\)Lu-PSMA-617 was lower than for \(^{177}\)Lu-PSMA-I&T (0.77 Gy/GBq vs 0.92 Gy/GBq, p=0.0015). Both PSMA small molecules demonstrated a comparable dose to parotid glands (0.5 Gy/GBq, p=0.27). Among all normal organs, lacrimal glands exhibited the highest mean absorbed dose of 5.1 Gy/GBq and 3.7 Gy/GBq for \(^{177}\)Lu-PSMA-617 and \(^{177}\)Lu-PSMA I&T, respectively. All tumor metastases exhibited a higher initial uptake when using \(^{177}\)Lu-PSMA I&T, as well as shorter tumor half-life as compared to \(^{177}\)Lu-PSMA-617 (p<0.00001). The mean absorbed tumor doses were comparable for both \(^{177}\)Lu-PSMA I&T and \(^{177}\)Lu-PSMA-617 (5.8 Gy/GBq vs. 5.9 Gy/GBq, p=0.96). All patients tolerated the therapy without any acute adverse effects. There was a small, statistically significant reduction in hemoglobin, leukocyte counts and platelet counts after \(^{177}\)Lu-PSMA-617 and \(^{177}\)Lu-PSMA I&T which did not need any clinical intervention. No nephrotoxicity was observed after either \(^{177}\)Lu-PSMA I&T or \(^{177}\)Lu-PSMA-617 PRLT. **Conclusions:** Both \(^{177}\)Lu-PSMA I&T and \(^{177}\)Lu-PSMA-617 PRLT demonstrated favorable safety in mCRPC patients. Highest absorbed dose amongst healthy organs were observed for the lacrimal and parotid glands, however, not resulting in any significant
clinical sequel. $^{177}$Lu-PSMA-617 demonstrated higher whole-body and lacrimal glands absorbed dose, but lower renal doses as compared to $^{177}$Lu-PSMA-I&T. The mean absorbed tumor doses were comparable for both $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617. There was a large inter-patient variability of the dosimetry parameters. Therefore, individual patient-based dosimetry seems favorable for personalized PRLT.

**Key Words:** prostate-specific membrane antigen (PSMA), dosimetry, $^{177}$Lu, PSMA radioligand therapy (PRLT), $^{177}$Lu-PSMA I&T, $^{177}$Lu-PSMA-617, theranostics
INTRODUCTION

Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death in men; in 2020, there were almost 1.4 million new cases and 375,000 deaths worldwide (1). It carries a poor prognosis when it metastasizes aggressively after initial treatment and becomes castration-resistant (2).

A promising treatment modality in the management of metastatic castration-resistant prostate cancer (mCRPC) can be provided after prostate-specific membrane antigen (PSMA) small molecules are radiolabeled; such PSMA-targeted radioligand therapy (PRLT) may employ the β-emitting radionuclide lutetium-177 (Lu) and/or the α-emitter actinium-225 (Ac), as per multiple retrospective studies. 177Lu-PSMA therapy decreased prostate-specific antigen (PSA) by at least 50% in 32/50 men with mCRPC who had progressed following conventional treatment while demonstrating a favorable toxicity profile (3,4). In a randomized, open-label, phase 2 trial, TheraP, 177Lu-PSMA therapy produced a higher PSA response and fewer adverse events than had cabazitaxel chemotherapy in mCRPC (5). Furthermore, 225Ac-PSMA targeted alpha therapy has provided durable disease control after failure of 177Lu-PSMA treatment, when all other therapeutic options had been exhausted (6-10).

Currently, the most frequently used PSMA-targeting small molecule inhibitors are DOTA-PSMA-617 (PSMA-617) and DOTAGA-PSMA-I&T (PSMA-I&T); prefixes DOTA and DOTAGA denote the cages enclosing the radionuclides and the suffix “I&T” denotes the radionuclide that yields both imaging and therapy). 177Lu (half-life = 6.7 days) is the radionuclide for theranostics, as it emits a cytotoxic β-particle for effective therapy and also the ability to quantify γ-emission enabling diagnostic evaluation and biodistribution using scintigraphy for dosimetry.

Pilot dosimetric studies of either 177Lu-PSMA-617 or 177Lu-PSMA-I&T were performed to estimate the absorbed doses for normal organs and tumor lesions. An initial study included seven patients in which the pretreatment radiation doses were estimated using a tracer amount of 177Lu-PSMA-617, indicated that the dose-limiting organ seemed to be the parotid glands rather than kidneys, and that the radiation dose to the bone marrow was significantly lower than those for kidneys and the parotid glands (11). These dosimetric studies were obtained in a small number of patients, however, and were given in tracer amounts...
or low therapeutic activity; indeed, few publications have addressed the absorbed doses delivered to tumors after 177Lu-PSMA radionuclide therapy, and dosimetric approaches for calculation of the absorbed doses have varied between studies (11-19).

Therefore, for the first time, we compared 177Lu-PSMA-617 and 177Lu-PSMA-I&T by using the identical dosimetry protocol. The Bad Berka Dose protocol (BBDP), used in our daily clinical routine, has been established during more than 15 years in the treatment of more than 1,000 neuroendocrine neoplasm patients undergoing peptide receptor radionuclide therapy (PRRT) (20,21). Dosimetric parameters, such as uptake and estimated mean absorbed dose to organs and tumour lesions, were obtained from these dosimetric calculations to evaluate therapeutic response as well as possible adverse effects.

For this reason, the aim of this study was to determine the safety, kinetics and dosimetry of 177Lu labelled PSMA small molecules 177Lu-PSMA-I&T and 177Lu-PSMA-617 in a large cohort of patients with mCRPC undergoing PSMA radioligand therapy under the identical dosimetry protocol.

MATERIALS AND METHODS

Patients

A total of 138 patients (mean age, 70±9 y; age range 46-90 y) with progressive mCRPC who received 177Lu-PSMA-I&T or 177Lu-PSMA-617 PRLT at Zentralklinik Bad Berka (Germany) were enrolled in this retrospective study. Significant PSMA expression of the metastases was confirmed by a 68Ga-PSMA-11 PET/CT (Siemens Biograph mCT Flow 64). The demographics of the patients and the location of metastases are shown in Table 1.

177Lu-PSMA I&T and 177Lu-PSMA-617 were administered in compliance with the German Medicinal Products Act, AMG §13 2b, and in accordance with the responsible regulatory body (the “Thüringer Landesamt”, i.e. the government of Thuringia). All patients underwent PRLT under the “compassionate use” clause of the German Medicinal Product Act (22). All procedures performed in studies involving human participants complied with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical
standards. The decision to perform PRLT was based on the decision of the referring physicians (urologists and oncologists) based on the exhaustion of all conventional therapy options and also taking into account age, renal function, and adverse effects of possible other therapies. The study protocol was approved by the local ethics committee (No. 34333/2017/96. Bad Berka, Germany). All patients signed a detailed written informed consent form before undergoing the treatment, as well as consenting to the use of their anonymized clinical data for scientific purposes. The administered activities are shown in Table 1.

Radiopharmaceuticals and Infusion

$^{177}$Lu labelling of the DOTAGA-based PSMA ligand PSMA-I&T (DOTAGA-(I-y)fk(Sub-KuE)) and the PSMA-617 ligand was performed in our GMP-certified radiopharmacy using previously published methods (23,24). 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. The reaction solutions were diluted with saline to achieve a suitable volume. After sterile filtration, a sample was taken for quality control (radio-HPLC, radio-TLC, pH, LAL, sterility testing, retention sample). Radiochemical purity was more than 95% in all cases (in most labelling procedures, >99 %). The radiopharmaceutical was administered intravenously over 10–15 min by using a dedicated infusion pump system for radionuclide therapy.

Imaging and Dosimetry

Dose estimation requires an accurate determination of the time-dependent activity of the organs and tumours. Thus, most important is the correct evaluation of the distribution and the kinetics of the administered radiopharmaceutical (25,26). To do so, we adapted the calculation model to our special conditions to establish the BBDP which is practicable in daily clinical routine and to make dosimetry available for each patient. The dosimetric approach is based on the MIRD-scheme and mean absorbed doses are estimated using the software OLINDA 2.0 (27-30). The workflow of the BBDP is shown in Figure 1.

At least five serial planar whole body (WB) scintigraphics and one SPECT/CT were acquired per patient. For planar WB imaging, we used the following gamma camera settings: MEDISO spirit DH-V dual-
headed gamma camera (Medical Imaging Systems, Budapest, Hungary), MeGP collimator, 15 % energy window, peak at 208 keV, scan speed 15 cm/min. WB scintigraphies were acquired at the following time points post injection (p.i.): from 0.5 h p.i. (immediately after administration of therapeutic activity and before bladder voiding) up to 68 h p.i. with a total of at least 5 time points. Additionally, post-therapy SPECT/CT images of kidneys and/or tumour-involved regions was done at 24, 48 or 72 h p.i. using a Siemens Symbia T camera system (Siemens Healthcare GmbH, Erlangen, Germany) with the following settings: MELP collimator, peak at 113 keV and 208 keV (15 % energy windows and 20 % upper and lower scatter window), 128x128 matrix, 32 projections with 30 s per step, body contour.

Because the patients were not allowed to empty the bladder before the first scan, the total body counts acquired immediately after the injection were defined to be 100 % of the administered activity. By assessing means of regions of interest (ROIs), which were drawn manually over the source regions, the scintigraphies were analysed using the HERMES system (Hermes Medical Solutions, Stockholm, Sweden). ROIs were always drawn manually by the same physicist, in collaboration with a nuclear medicine physician, who decided which lesions were suitable for dosimetry; preferably, these “target lesions” had the highest uptake in each organ. The SPECT/CT scans were reconstructed and quantified using the HERMES SUV SPECT software (HERMES Medical Solutions, Stockholm, Sweden). Mean absorbed organ and tumour doses were estimated using OLINDA 2.0. Specifically, mean absorbed tumour doses and mean absorbed doses of parotid and lacrimal glands were estimated by using the unit density sphere module of OLINDA 2.0. A standard volume was used to assess lacrimal glands, according to the study of Bingham et. al. (31).

By following this described dosimetry protocol, the following parameters were assessed: uptake as fraction of administered activity (%IA), effective half-life (hours), and mean absorbed organ and tumour doses (Gy/GBq). Organs showing tumour involvement were excluded from dosimetric evaluation.

**Toxicity Assessment**

All patients were clinically monitored during therapy and for at least 2–4 days thereafter as inpatients for possible side effects. Vital parameters were recorded during therapy and a structured
questionnaire documented any delayed complication. Laboratory analysis including hematologic status, renal function, and liver function was performed before each PRLT cycle and in follow-up (restaging was performed regularly until death). Treatment-related adverse events were recorded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

**Statistical Analysis**

All dosimetric parameters were determined for whole body and normal organs (kidneys, parotid glands and lacrimal glands) as well as for metastases. Results are given as median values. For the comparison of two $^{177}$Lu labeled PSMA ligands, the following parameters were chosen to describe the differences between the peptides: uptake at 20 h p.i., effective half-life, and mean absorbed dose. Nonparametric tests for independent samples were used to describe significant differences among the ligands. All statistical tests were performed on ORIGIN PRO 8.1G; p-values of less than 0.05 were considered significant.

**RESULTS**

For both $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617, physiologic uptake was observed in the lacrimal and salivary glands, kidneys, and small intestine, exhibiting strong physiological accumulation on the post-therapy scans, followed by medium to low uptake in the liver and spleen at all time points. The radiopharmaceutical was predominantly excreted through the kidneys, as visualized by the accumulation in the urinary bladder that was dominant on the early scans 0.5 and 3 h p.i. Excellent uptake and retention of $^{177}$Lu-PSMA I&T as well as $^{177}$Lu-PSMA-617 was noted in metastases and residual/locally recurrent prostate cancer on post-therapy planar and SPECT/CT images (Figure 2).

**Whole body**

A higher retention of $^{177}$Lu-PSMA-617 was observed at all time points as compared to $^{177}$Lu-PSMA I&T. The curves demonstrate an initial rapid wash-out followed by a second slower decline. On that account,
the time activity curves for WB were fitted to a bi-exponential function. The half-lives were shorter for 
$^{177}$Lu-PSMA I&T (35 h) as compared to $^{177}$Lu-PSMA-617 (42 h). As the result of calculations from these
kinetic parameters, the WB mean absorbed dose was higher for $^{177}$Lu-PSMA-617 as compared to $^{177}$Lu-
PSMA I&T (0.04 Gy/GBq vs 0.03 Gy/GBq, p<0.00001) (Figure 3).

Kidneys

We analysed renal kinetics and kidney dosimetry of the 51 patients treated with $^{177}$Lu-PSMA I&T
and the 83 patients treated with $^{177}$Lu-PSMA-617. The renal uptake was marginally higher for $^{177}$Lu-PSMA
I&T. For both ligands, the uptake showed a rapid decline between the first scan and 3 h p.i., followed by a
slower wash-out with longer half-life of $^{177}$Lu-PSMA-617. The effective renal half-life for $^{177}$Lu-PSMA-
617 and $^{177}$Lu-PSMA I&T were 40 h and 33 h, respectively (p=0.00511). As compared to $^{177}$Lu-PSMA-617,
the residence time was longer for $^{177}$Lu-PSMA I&T (p=0.00138) with initially higher uptake (p<0.00001),
and the resulting renal dose was slightly, but statistically significantly higher for $^{177}$Lu-PSMA I&T.
Calculated radiation-absorbed doses of kidneys for $^{177}$Lu-PSMA-617 and $^{177}$Lu-PSMA I&T were 0.8
Gy/GBq and 0.9 Gy/GBq, respectively (p=0.0015).

Parotid and lacrimal glands

Parotid glands were analysed in 47 patients treated with $^{177}$Lu-PSMA I&T and 80 patients with
$^{177}$Lu-PSMA-617. Both ligands demonstrated a first increase of activity until 3 h p.i. before the exponential
wash-out, while $^{177}$Lu-PSMA-617 showed higher uptake values and longer half-lives. The effective half-
life of parotid glands for $^{177}$Lu-PSMA-617 and $^{177}$Lu-PSMA I&T were 31 h and 23 h, respectively
(p<0.00001); yet, the mean absorbed dose of the different ligands was comparable in parotid glands (0.5
Gy/GBq) (p=0.26603) (Figure 3).

Lacrimal glands were analysed in 42 patients treated with $^{177}$Lu-PSMA I&T and in 69 patients
treated with $^{177}$Lu-PSMA-617. The uptake was slightly higher and the half-life was longer for $^{177}$Lu-PSMA-
617. Effective half-life for $^{177}$Lu-PSMA-617 and $^{177}$Lu-PSMA I&T were 28 h and 25 h, respectively
(p=0.00269). The resulting absorbed dose to the lacrimal glands was significantly higher for $^{177}$Lu-PSMA-
617 as compared to $^{177}$Lu-PSMA I&T (5.1 Gy/GBq vs 3.7 Gy/GBq, p=0.000617). Notably, among all normal organs, the lacrimal glands exhibited the highest absorbed doses - 31 Gy and 22 Gy for $^{177}$Lu-PSMA-617 and $^{177}$Lu-PSMA I&T, respectively for an injected activity of 6 GBq.

**Tumour dosimetry**

$^{177}$Lu-PSMA I&T exhibited a higher initial uptake as compared to $^{177}$Lu-PSMA-617 (Figure 4). All time activity curves were fitted to mono-exponential functions from 20 h p.i., which led to significantly longer half-lives for $^{177}$Lu-PSMA-617. Similar to the results in normal organs, the effective half-life in metastases was longer for $^{177}$Lu-PSMA-617 ($T_{1/2} = 61$ h) than for $^{177}$Lu-PSMA I&T ($T_{1/2} = 43$ h, p<0.00001). The mean absorbed tumor doses extended over a high range, while the medians of the mean absorbed tumor doses were comparable ($^{177}$Lu-PSMA-617 vs. $^{177}$Lu-PSMA I&T $= 5.9$ Gy/GBq vs. 5.8 Gy/GBq, p=0.96257) (Figure 5).

Bone and lymph node lesions were considered separately because most of the investigated lesions were bone or lymph node metastases. After the administration of the therapeutic activity, the early elimination phase was different for the two ligands, demonstrating higher initial uptakes and faster wash-out for $^{177}$Lu-PSMA I&T in bone and lymph node lesions (Figure 4). $^{177}$Lu-PSMA-617 demonstrated a longer effective half-life in bone metastases than $^{177}$Lu-PSMA I&T (60 h vs. 43 h, p<0.00001) as well as in lymph node metastases (55 h vs. 42 h, p=0.0275). However, the mean absorbed doses of bone metastases were comparable ($^{177}$Lu-PSMA-617 vs. $^{177}$Lu-PSMA I&T $= 6.0$ Gy/GBq vs. 5.9 Gy/GBq, p=0.82564), as were the doses for lymph node metastases ($^{177}$Lu-PSMA-617 vs. $^{177}$Lu-PSMA I&T $= 7.1$ Gy/GBq vs. 6.9 Gy/GBq, p=0.94015). For both ligands, the mean absorbed tumour dose was higher for lymph node lesions as compared with bone lesions (Figure 5). The mean absorbed tumour to kidney dose ratio is slightly higher for $^{177}$Lu-PSMA-617 (7.6) as compared to $^{177}$Lu-PSMA I&T (6.3).

**Treatment Toxicity**

There were no serious acute, short-term (after 2 cycles of PRLT), or long-term follow-up (after 2-6 cycles of PRLT with follow-up according to the last restaging, observation period, 3.2-48.5 months,
mean±SD, 17.4±11.9 months, median, 13.2 months) adverse effects in all patients receiving either $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617. No change in blood pressure, heart rate or body temperature was observed during therapy. The most common adverse effect was mild fatigue, which was observed in 20% of the patients lasting a few days after therapy, more frequently after the 1st cycle. Five patients (3.6%) reported mild, reversible xerostomia - two patients (3.9%) in the $^{177}$Lu-PSMA I&T group and 3 (3.4%) in $^{177}$Lu-PSMA-617 group, after 2-6 cycles of treatment and in follow-up. Xerophthalmia was not reported by any of the patients. No other adverse symptoms were noticed during the entire follow-up period.

Hematotoxicity and nephrotoxicity after $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617 PRLT are detailed in Table 2, Table 3 and Figure 6. There was no evidence of renal toxicity after either $^{177}$Lu-PSMA I&T or $^{177}$Lu-PSMA-617 PRLT, as determined by serum creatinine, creatinine clearance using the Cockcroft–Gault formula, or tubular extraction rate as determined by $^{99m}$Tc-mercaptoacetyltriglycine (MAG3) renal scintigraphy which was scanned before therapy and then 3-monthly for follow-up. No CTCAE grade 3 or 4 nephrotoxicity was observed during any treatment cycle and during longer follow up. There was a small, statistically significant reduction in hemoglobin, leukocyte counts and platelet counts after $^{177}$Lu-PSMA-617 and $^{177}$Lu-PSMA I&T (Figure 6), although the absolute differences were minimal and clinically insignificant. Remarkably, patients with low blood cell counts before therapy did not exhibit a decrease in blood cell counts after either $^{177}$Lu-PSMA I&T or $^{177}$Lu-PSMA-617 therapy.

DISCUSSION

Through this study of a large cohort of mCRPC patients treated in a single centre, we used the identical dosimetry protocol when depicting biodistribution and results of dosimetric analyses obtained after either $^{177}$Lu-PSMA I&T or $^{177}$Lu-PSMA-617 PRLT therapy.

$^{177}$Lu-PSMA-617 exhibited a higher mean absorbed dose for whole body and lacrimal glands and showed longer half-lives in all normal organs as well as in tumour lesions – the highest tumour doses were estimated for lymph node lesions. $^{177}$Lu-PSMA I&T exhibited a higher initial tumour uptake as compared
to $^{177}$Lu-PSMA-617. The mean absorbed tumor doses extended over a high range, while the median of the mean absorbed tumor doses were comparable for both $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617.

The dose estimations for $^{177}$Lu-PSMA-617 revealed a mean absorbed dose of 0.8 Gy/GBq for kidneys, 0.4 Gy/GBq for parotid glands and 5.1 Gy/GBq for lacrimal glands (median values). Comparable results were reported by Zechmann et al. after they performed dosimetric estimations with iodine-131 labelled PSMA ligands (32). Kabasakal et al. reported comparable organ doses in seven patients, who had received a pre-therapeutic dose of $^{177}$Lu-PSMA-617. The dosimetric approach employed was based on planar imaging, to which attenuation correction was applied using PET/CT images (11). Delker et al. also evaluated dosimetry of $^{177}$Lu-PSMA-617 in five patients using whole body scans and quantitative SPECT/CT. They estimated a slightly lower renal dose of 0.6 Gy/GBq compared to 0.8 Gy/GBq in the current study. Similarly, 1.4 Gy/GBq were reported for parotid glands compared to 1.6 Gy/GBq in our study (mean values). Delker et al. reported mean absorbed tumour doses in five patients in the range of 1.2-47.5 Gy (14). In the current study, with a much larger patient population, we found a wider range of mean absorbed tumour doses (between 1.0 and 670 Gy per cycle for individual patients). The highest tumour absorbed doses of 670 Gy was achieved in the lymph node metastasis in a mCRPC patient with lymph node and liver metastases during his second cycle of PRLT with 6.0 GBq $^{177}$Lu-PSMA-617.

The major route of excretion of both $^{177}$Lu labelled PSMA ligands is through the kidneys as noted by the predominant urinary excretion in the bladder. The high uptake in the kidneys may be due to PSMA expression in renal tissue, however, for substantial uptake of the radiopharmaceutical was noticed especially on the early $^{177}$Lu PSMA post-therapy images. Blocking of specific PSMA binding in the kidney tissue by PMPA has been validated in pre-clinical studies, but this compound currently has limited availability for clinical use and also blocks tumour uptake (33). There was no evidence of renal toxicity after either $^{177}$Lu-PSMA-617 or $^{177}$Lu-PSMA-I&T PRLT, inasmuch as there was no significant change in serum creatinine, in creatinine clearance as obtained by Cockcroft-Gault formula, or in tubular extraction rate as determined by Tc-99m MAG3 renal scintigraphy.
According to the presented dosimetry results, we summarized the maximum amount of activity as well as number of possible therapy cycles to reach dose limits for both PSMA ligands (Supplemental Table 1). Regarding parotid glands, the maximum number of therapy cycles is 16 or 18 to reach dose limit, assuming an injected activity of 6 GBq $^{177}$Lu-PSMA I&T or $^{177}$Lu-PSMA-617 per cycle, respectively. The renal dose on the other hand would limit the number of cycles to four in case of $^{177}$Lu-PSMA I&T, and five in case of $^{177}$Lu-PSMA-617 – if the “23 Gy rule”, as known from external beam radiotherapy, would be employed (34). However, the high number of cycles according to the current dose limit derived from the external beam radiotherapy may not reflect the true clinical status of the patients after radionuclide therapy. The absorbed dose of parotid glands in those patients who reported mild, reversible xerostomia in the present study were still under the dose limit. More therapy cycles with accumulative dose over the absorbed dose limit of 23 Gy were feasible without any relevant side effects to the kidneys. Therefore, the limit for renal dose from external beam radiotherapy may not apply for PRLT.

Despite the longer effective half-life and longer residence time of $^{177}$Lu-PSMA-617 in metastases as compared to $^{177}$Lu-PSMA I&T, the resulting mean absorbed tumor doses were not significantly different for these two ligands. This result is most probably due to the higher initial uptake of $^{177}$Lu-PSMA I&T as compared to $^{177}$Lu-PSMA-617. In addition, non-homogeneous distributed sample of metastases in both patient cohorts could have taken influence as the median volume of metastases was lower for patients treated with PSMA I&T (median volume = 3 ml) as for those patients receiving PSMA-617 radioligand therapy (median volume = 6 ml). When comparing lesions with similar residence time, smaller lesion will get the higher mean absorbed dose.

For the dosimetry results, high interpatient variability was found, especially concerning the mean absorbed doses; this was not unexpected since it was a very heterogeneous group of patients was studied. In addition, earlier results from a PRRT study also demonstrated a high intra-patient variability in patients undergoing therapy with different peptides; even in a large cohort of patients, we found a broad range of results (20,21). This implies that the median or mean value of a dosimetric parameter varies among patients.
Although the variability may be attributed to the difference in the biological behaviour of the different ligands, it may be also ascribable to widely differing prior therapies.

This study suffers from a few limitations, e.g., retrospective design. No strict pretest criteria for the selection of patients were applied, and the baseline characteristics for the two groups were heterogeneous. Additionally, the wide interpatient variability should be addressed in further studies: inasmuch as significant variations were found even in the large cohort of patients, median values of absorbed doses among patients should not be the only criterion for planning PRLT. Beside the described methods for individual dosimetry, inter-individual differences should be taken into account.

CONCLUSION

Both $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617 PRLT demonstrated favorable safety in mCRPC patients. Highest absorbed dose amongst healthy organs were observed for the lacrimal and parotid glands, however, not resulting in any significant clinical side effects. $^{177}$Lu-PSMA-617 showed longer half-lives in all normal organs as well as tumour lesions than $^{177}$Lu-PSMA I&T. $^{177}$Lu-PSMA I&T exhibited a higher initial tumour uptake as compared to $^{177}$Lu-PSMA-617. The mean absorbed tumor doses were comparable for both $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617. The results of this study further demonstrate that the estimation of mean absorbed doses to critical organs and tumour lesions is necessary when evaluating the risks of PRLT and, therefore, when describing the clinical benefit to the patient. Individual patient-based dosimetry seems favorable for personalized PRLT.

DISCLOSURE

No potential conflicts of interest relevant to this article exist.

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KEY POINTS

QUESTION: Do $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617 differ in safety, biodistribution and dosimetry for PSMA radioligand therapy in patients with metastatic castration-resistant prostate cancer (mCRPC)?

PERTINENT FINDINGS: In a large cohort of 138 patients with mCRPC undergoing PSMA radioligand therapy under the identical dosimetry protocol, $^{177}$Lu-PSMA-617 showed longer half-lives in all normal organs as well as tumour lesions; $^{177}$Lu-PSMA I&T exhibited a higher initial tumour uptake as compared to $^{177}$Lu-PSMA-617. The mean absorbed tumor doses were comparable for both $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617.

IMPLICATIONS FOR PATIENT CARE: The results of this study further demonstrate that the estimation of mean absorbed doses to critical organs and tumour lesions is necessary when evaluating the risks of PRLT and, therefore, when describing the clinical benefit to the patient.
REFERENCES


Table 1: Demographic and baseline characteristics of patients with mCRPC (n = 138)

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<td>n (%)</td>
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<tr>
<td>Number of patients</td>
<td>138</td>
<td>51</td>
<td>87</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70±9 (range, 46–90)</td>
<td>71±9 (range, 46–87)</td>
<td>69±9 (range, 50–90)</td>
</tr>
<tr>
<td>ISUP Grading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade Group 1</td>
<td>7 (5.1%)</td>
<td>2 (3.9%)</td>
<td>5 (5.7%)</td>
</tr>
<tr>
<td>Grade Group 2</td>
<td>20 (14.5%)</td>
<td>3 (5.9%)</td>
<td>17 (19.5%)</td>
</tr>
<tr>
<td>Grade Group 3</td>
<td>21 (15.2%)</td>
<td>10 (19.6%)</td>
<td>11 (12.6%)</td>
</tr>
<tr>
<td>Grade Group 4</td>
<td>26 (18.8%)</td>
<td>6 (11.8%)</td>
<td>20 (23.0%)</td>
</tr>
<tr>
<td>Grade Group 5</td>
<td>39 (28.3%)</td>
<td>18 (35.3%)</td>
<td>21 (24.1%)</td>
</tr>
<tr>
<td>NA</td>
<td>25 (18.1%)</td>
<td>12 (23.5%)</td>
<td>13 (14.9%)</td>
</tr>
<tr>
<td>PSA Level (ng/mL)</td>
<td>216.5±538.7</td>
<td>90.6±158.7</td>
<td>283.3±648.2</td>
</tr>
<tr>
<td>Metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes Mts.</td>
<td>109 (79.0%)</td>
<td>38 (74.5%)</td>
<td>71 (81.6%)</td>
</tr>
<tr>
<td>Bone Mts.</td>
<td>108 (78.2%)</td>
<td>39 (76.5%)</td>
<td>69 (79.3%)</td>
</tr>
<tr>
<td>Bone marrow Mts.</td>
<td>11 (8.0%)</td>
<td>2 (3.9%)</td>
<td>9 (10.3%)</td>
</tr>
<tr>
<td>Lung Mts.</td>
<td>15 (10.9%)</td>
<td>6 (11.8%)</td>
<td>9 (10.3%)</td>
</tr>
<tr>
<td>Liver Mts.</td>
<td>12 (8.7%)</td>
<td>4 (7.8%)</td>
<td>8 (9.2%)</td>
</tr>
<tr>
<td>other Mts.</td>
<td>36 (26.1%)</td>
<td>10 (19.6%)</td>
<td>26 (29.9%)</td>
</tr>
<tr>
<td>Injected activity (GBq)</td>
<td>6.4±1.0 (range, 3.4–9.0)</td>
<td>6.1±1.0 (range, 3.4–7.6)</td>
<td>6.5±1.1 (range, 3.5–9.0)</td>
</tr>
</tbody>
</table>

mCRPC = metastatic castration-resistant prostate cancer. ISUP = International Society of Urological Pathology. NA = not available. PSA = prostate-specific antigen. Mts. = metastases;
Table 2. Hematotoxicity and nephrotoxicity after $^{177}$Lu-PSMA I&T PRLT according to CTCAE v.5.0. ($n = 35$)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Anemia</th>
<th>Leukocytopenia</th>
<th>Thrombocytopenia</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-therapy</td>
<td>After 2 cycles</td>
<td>Long-term FU</td>
<td>Pre-therapy</td>
</tr>
<tr>
<td>CTC-1</td>
<td>21</td>
<td>30</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>CTC-2</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>CTC-3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CTC-4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTC-5</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

CTCAE v.5.0 = The National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. PRLT = PSMA radioligand therapy. CTC = Common Terminology Criteria grade. NA = not applicable before therapy (grade 5 represents death). FU = follow up.
Table 3. Hematotoxicity and nephrotoxicity after $^{177}$Lu-PSMA-617 PRLT according to CTCAE v.5.0. ($n = 66$)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Anemia</th>
<th>Leukocytopenia</th>
<th>Thrombocytopenia</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-therapy</td>
<td>After 2 cycles</td>
<td>Long-term FU</td>
<td>Pre-therapy</td>
</tr>
<tr>
<td>CTC-1</td>
<td>44</td>
<td>45</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>CTC-2</td>
<td>7</td>
<td>14</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>CTC-3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTC-4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTC-5</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

CTCAE v.5.0 = The National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. PRLT = PSMA radioligand therapy. CTC = Common Terminology Criteria grade. NA = not applicable before therapy (grade 5 represents death). FU = follow up.
**Figure 1** Flowchart of the Bad Berka Dose Protocol

*Hermes Medical Solutions, Stockholm, Sweden*
Figure 2 PRLT post-therapy scans and SPECT MIP image: (A) scans after $^{177}$Lu-PSMA I&T; (B) scans after $^{177}$Lu-PSMA-617.
Figure 3 Biodistribution and dosimetry results of normal organs in patients treated with different PSMA ligands: (A) Kinetics-Median uptakes in %IA; (B) Median effective half-life in hours; (C) Median residence time in hours; (D) Mean absorbed doses in Gy/GBq.
Figure 4 Kinetics of metastases and comparative results from 96 metastases (bone, lymph node, liver, lung and other) of patients treated with $^{177}$Lu-PSMA I&T and 179 tumour lesions (bone, lymph node, liver, lung and other) of patients treated with $^{177}$Lu-PSMA-617: (A) Median kinetics of all types of metastases; (B) Median kinetics of bone metastases; (C) Median kinetics of lymph node metastases. After the administration of the therapeutic activity, higher initial uptakes and faster wash-out for $^{177}$Lu-PSMA I&T were observed in bone and lymph node lesions. In contrast, the curves of $^{177}$Lu-PSMA-617 showed an initial increase until 3 h p.i.
**Figure 5** Comparative dosimetry results of metastases: (A) Median effective half-life; (B) Median residence time; (C) Mean absorbed dose.
Figure 6 Comparison of laboratory parameters (hemoglobin; leukocyte; platelet; serum creatinine) before (left: pre-therapy), after 2 cycles of treatment (middle: after 2 cycles), and after 2-6 cycles of treatment with long-term follow up (right: long-term FU; observation period, 3.2 - 48.5 months, mean ± SD, 17.4 ± 11.9 months, median, 13.2 months) after $^{177}$Lu-PSMA I&T (n=35) and $^{177}$Lu-PSMA-617 PRLT (n=66). FU = follow up.
Implications:
In a large cohort of 138 patients with mCRPC undergoing PSMA radioligand therapy under the identical dosimetry protocol, $^{177}$Lu-PSMA-617 showed longer half-lives in all normal organs as well as tumour lesions. $^{177}$Lu-PSMA I&T exhibited a higher initial tumour uptake as compared to $^{177}$Lu-PSMA-617. The mean absorbed tumor doses were comparable for both $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617.
SUPPLEMENTARY DATA

MATERIALS AND METHODS

Imaging and Dosimetry

After segmentation, the SPECT activity of source regions was used to scale the time-activity curves obtained from planar imaging. In the next step, these time-activity curves were fitted to mono- or bi-exponential functions to calculate effective half-lives and the time-integrated activity coefficient. Mean absorbed organ and tumour doses were estimated using OLINDA 2.0. For normal organs, the IRCP 89 adult male model included in OLINDA 2.0 was used. Volumes of normal organs and metastases were obtained by the CT of the patient from SPECT/CT scans by using a Siemens Symbia T camera system (Siemens Healthcare GmbH, Erlangen, Germany) with the following settings: MELP collimator, peak at 113 keV and 208 keV (15 % energy windows and 20 % upper and lower scatter window), 128x128 matrix, 32 projections with 30 s per step, body contour; CT: 130 kV, 5mm slices, CAREDOSE.

Supplemental Table 1 Maximum amount of activity and number of possible therapy cycles to reach dose limits for both PSMA ligands according to the current organ radiation-absorbed dose constraints

<table>
<thead>
<tr>
<th></th>
<th>Whole Body</th>
<th>Kidneys</th>
<th>Parotid glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ radiation-absorbed dose constraints (Gy)</td>
<td>2</td>
<td>23</td>
<td>52</td>
</tr>
<tr>
<td>Maximum amount of activity to reach dose limit for $^{177}$Lu-PSMA I&amp;T (GBq)</td>
<td>73</td>
<td>25</td>
<td>96</td>
</tr>
<tr>
<td>Number of possible cycles to reach dose constraints, activity per cycle = 6 GBq $^{177}$Lu-PSMA I&amp;T</td>
<td>12</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Maximum amount of activity to reach dose limit for $^{177}$Lu-PSMA-617 (GBq)</td>
<td>52</td>
<td>30</td>
<td>109</td>
</tr>
<tr>
<td>Number of cycles of possible cycles to reach dose constraints, activity per cycle = 6 GBq $^{177}$Lu-PSMA-617</td>
<td>9</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>