Research Square

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Kidney absorbed radiation doses for [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T determined by 3D clinical dosimetry

Maike J.M. Uijen
Radboudumc
Bastiaan Michael Privé (bastiaan.prive@radboudumc.nl)
Radboudumc https://orcid.org/0000-0002-4056-9117
Carla M.L. Van Herpen
Radboudumc
Harm Westdorp
Radboudumc
Willemijn A. van Gemert
Radboudumc
Maarten de Bakker
Radboudumc
Martin Gotthardt
Radboudumc
Mark Konijnenberg
Radboudumc
Steffie M.B. Peters
Radboudumc
James Nagarajah
Radboudumc

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Abstract

Purpose: For prostate-specific membrane antigen directed radioligand therapy (PSMA-RLT), [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T are the currently preferred compounds. Recent preclinical studies suggested ~30x higher kidney absorbed dose for [^{177}Lu]Lu-PSMA-I&T compared to [^{177}Lu]Lu-PSMA-617, which may lead to an increased risk of kidney toxicity. We performed two single center, prospective dosimetry studies with either [^{177}Lu]Lu-PSMA-617 or [^{177}Lu]Lu-PSMA-I&T, using an identical dosimetry protocol. We evaluated the absorbed doses of both ^{177}Lu labeled radioligands in human kidneys.

Methods: 3D SPECT/CT imaging of the kidneys was performed after PSMA-RLT in cancer patients with PSMA-positive disease and an adequate glomerular filtration rate (GFR) (≥50 mL/min). Ten metastatic hormone-sensitive prostate cancer patients (mHSPC) were treated with [^{177}Lu]Lu-PSMA-617 and ten advanced salivary gland cancer (SGC) patients were treated with [^{177}Lu]Lu-PSMA-I&T. SPECT/CT imaging was performed at 5 time points (1h, 24h, 48h, 72h, and 168h post injection). In mHSPC patients SPECT/CT imaging was performed after cycles 1 and 2 (cumulative activity: 9 GBq) and in SGC patients only after cycle 1 (activity: 7.4 GBq). Kidney absorbed dose was calculated using organ-based dosimetry.

Results: The median kidney absorbed dose was 0.49 Gy/GBq (range: 0.34-0.66) and 0.73 Gy/GBq (range: 0.42-1.31) for [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T, respectively (Wilcoxon-Mann-Whitney; p=0.002).

Conclusion: This study shows that the kidney absorbed dose for [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T differs, with a ~1.5x higher median kidney absorbed dose for [^{177}Lu]Lu-PSMA-I&T. This difference in the clinical setting is considerably smaller than observed in preclinical studies and may not hamper treatments with [^{177}Lu]Lu-PSMA-I&T.

Introduction

Prostate-specific membrane antigen (PSMA) is a transmembrane protein and highly overexpressed by prostate cancer cells, which makes it an ideal target for theranostic application. PSMA-radioligand therapy (PSMA-RLT) with [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T showed promising response rates in metastatic castration-resistant prostate cancer (mCRPC) patients, with a favorable toxicity profile [1, 2]. Following these outcomes, PSMA-RLT is also studied for other PSMA expressing cancers, such as salivary gland cancer (SGC) [3, 4].

Unfortunately, the intestines, salivary glands, and proximal tubule of the kidneys also show high uptake of PSMA ligands, possibly resulting in significant radiation doses to these healthy organs following PSMA-RLT. Moreover, [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T are renally excreted, which may increase the radiation exposure to the kidneys even further. The European Guidelines also identified the kidneys as the most important dose-limiting organ for PSMA-RLT [5].

While kidney failure due to PSMA-RLT is rarely seen, this might also be the result of the poor overall survival of the end-stage patients that currently received PSMA-RLT. However, the number of trials that investigate PSMA-RLT in early-stage cancer patients is increasing (e.g. NCT04720157, NCT04430192, NCT04443062) [6, 7]. In these patients, late toxicities may become apparent during longer follow-up, such as kidney-related toxicities. Moreover, doses to the healthy organs such as the kidneys are important as organ toxicities could reduce the quality of life of patients and preclude patients from qualifying for following treatment lines.

Preclinical studies showed that kidney radiation doses with [^{177}Lu]Lu-PSMA-I&T are approximately 30 times higher compared to [^{177}Lu]Lu-PSMA-617 [8, 9]. This suggests an increased risk of kidney toxicity with [^{177}Lu]Lu-PSMA-I&T. However, these preclinical experiments were performed using *in vitro* and in murine models which do not directly translate to human kidneys.

Furthermore, in contrast to these preclinical findings, several clinical dosimetry studies found a comparable mean kidney absorbed radiation dose for ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T [10–17]. Unfortunately, these studies applied varying dosimetry protocols, often only using planar scans, and are therefore difficult to compare. Thus, it is presently unclear if patients receiving [^{177}Lu]LuPSMAI&T are exposed to higher kidney radiation doses compared to [^{177}Lu]Lu-PSMA-617. In this study, we compared the kidney dosimetry results of [^{177}Lu]Lu-PSMA-I&T and [^{177}Lu]LuPSMA617 which were acquired from two prospective clinical trials, following an identical 3D dosimetry protocol.

Material And Methods

Patients

In a third-line academic institute (Radboudumc, the Netherlands), two prospective clinical studies were conducted on PSMA-RLT in cancer patients with PSMA-positive disease and an adequate glomerular filtration rate (GFR) (≥ 50 mL/min). Both studies used an identical dosimetry protocol. One study applied a first cycle of 3 GBq and a second cycle (after 6 weeks) of ~ 6 GBq [^{177}Lu]Lu-PSMA-617 in ten low volume metastatic hormone-sensitive prostate cancer patients, thus in total a cumulative activity of ~ 9GBq [6]. The other used ~ 7.4 GBq [^{177}Lu]Lu-PSMA-I&T in ten advanced SGC patients (NCT04291300). The dosimetry protocol of both trials consisted of 5 time points (1h, 24h, 48h, 72h, and 168h) 3D SPECT/CT imaging post [^{177}Lu]Lu-PSMA injection. All scans were acquired on a Symbia T16 or Symbia Intevo Bold system (Siemens Healthineers, Erlangen, Germany).

Dosimetry analysis

The absorbed doses for both cohorts were calculated in a similar way, as previously described [18]. In short, volumetric organ-based dosimetry was performed according to the scheme defined by the Committee on Medical Internal Radiation Dose (MIRD) [19] using Hermes HybridViever/Dosimetry (Hermes Medical Solutions, Stockholm, Sweden). All SPECT/CT images were co-registered per patient,

followed by drawing volumes of interest (VOI) of the kidneys. Kidney absorbed radiation dose was determined in Olinda 2.1 (Hermes Medical Solutions, Stockholm, Sweden) using gender-specific human kidney weights based on the ICRP Publication 89 [20], corresponding S-values and a mono-exponential fit.

Statistical analysis

To test for baseline differences between study populations, the Wilcoxon-Mann–Whitney test was used for continuous variables and the Fisher's exact test was used for categorical variables. The Wilcoxon-Mann–Whitney test was used to compare the kidney absorbed radiation dose between [^{177}Lu]Lu-PSMA-617 treated mHSPC patients and [^{177}Lu]Lu-PSMA-I&T treated SGC patients. A pvalue < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, New York).

Results

A summary of both clinical studies is provided in table 1.

Patient characteristics

Per protocol, all 20 patients had had adequate kidney function at baseline (see table 2). The kidney uptake on baseline ^{68}Ga-PSMA-11 PET was also comparable between the two populations. The SGC patients had a significantly higher tumor burden than the low-volume mHSPC patients (p=<0.001). Figure 1 illustrates the baseline disease burden of 4 patients (2 mHSPC and 2 SGC). Furthermore, other baseline patient characteristics are presented in table 2.

Kidney absorbed radiation doses

Median kidney absorbed dose was 0.49 Gy/GBq (range: 0.34-0.66) for treatment with [^{177}Lu]Lu-PSMA-617, whereas the median kidney absorbed dose was 0.73 Gy/GBq (range: 0.42-1.31) for [^{177}Lu]Lu-PSMA-I&T (table 3). The difference in absorbed dose between [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T was statistically significant (p=0.004). As depicted in figure 2, apart from the initial higher kidney activity at the earliest time-points with [^{177}Lu]Lu-PSMA-I&T, both [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T show comparable kinetics over time. The median clearance half-lives were 26h (range: 15-43h) and 20h (range: 17-38h), for PSMA-617 and PSMA I&T, respectively (p=0.27).

Table 1: ^{177}Lu-PSMA treatment and dosimetry imaging

	mHSPC (*n*=10)	**SGC** (*n*=10)
PSMA ligand for PSMA-RLT	PSMA-617	PSMA-I&T
^{177}Lu-PSMA-RLT treatment	cycle 1: 3 GBq cycle 2: 6 GBq	2-4 cycles of 7.4 GBq
Dosimetry imaging	After cycle 1 + cycle 2	After cycle 1
Cumulative activity*	9 GBq	7.4 GBq
Dosimetry imaging timepoints (post-injection)†	1h 24h 48h 72h 168h	1h 24h 48h 72h 168h
Clinical study	NCT03828838	NCT04291300

Abbreviations: mHSPC: low-volume metastatic hormone-sensitive prostate cancer patients, SGC: salivary gland cancer patients, PSMA: prostate-specific membrane antigen, RLT: radioligand therapy, ^{177}Lu: lutetium-177, GBq: Giga-becquerel

*Total amount of activity for which dosimetry imaging data is available

†This included SPECT/CT imaging of the kidneys

Table 2: Baseline patient characteristics

	mHSPC (*n*=10) No. of pts (%)	SGC (*n*=10) No. of pts (%)	p-value
Gender			**0.033**
Male	10 (100)	5 (50)	
Female	0 (0)	5 (50)	
Age, median (range)	67 (61-77)	64 (51-74)	0.272
Disease burden			**<0.001**
≤10 tumor lesions	10 (100)	1 (10)	
>10 tumor lesions	0 (0)	9 (90)	
Kidney function*			
eGFR† (mL/min), median (range)	71 (61-88)	90 (61-90)	**0.005**
Kidney uptake ^{68}Ga-PSMA-11 PET*‡			
SUVmax, median (range)	60.5 (35.7-97.4)	59.4 (23.5-72.9)	0.496
SUVmean, median (range)	32.2 (16.9-51.2)	31.0 (12.1-40.0)	0.734
Median kidney VOI volume (mL) on SPECT/CT (range)	190 (130-250)	198 (160-295)	0.427

Abbreviations: mHSPC: low-volume metastatic hormone-sensitive prostate cancer patients, SGC: salivary gland cancer patients, eGFR: estimated glomerular filtration rate, ^{68}Ga: Gallium-68, PSMA: prostate-specific membrane antigen, PET: positron emission tomography, SUVmax: maximum standardized uptake value, SUVmean: mean standardized uptake value, VOI: volume of interest.

*Maximum time-interval between baseline kidney function assessment and baseline ^{68}Ga-PSMA-11 PET with the start of ^{177}Lu-PSMA RLT was 4 weeks.

†eGFR: based on the CKD-EPI equation.

‡Time interval between ^{68}Ga-PSMA injection and imaging was ±1 hour. ^{68}Ga-PSMA dose was 2.0 MBq/kg ± 10%, with a minimum of 20 Mbq and a maximum of 300 Mbq.

Table 3: Kidney absorbed doses per injected activity of [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T

Kidney absorbed dose (Gy/GBq)	mHSPC (n=10)	SGC (n=10)
	[^{177}Lu]Lu-PSMA-617	[^{177}Lu]Lu-PSMA-I&T
Median	0.49	0.73
Range	0.34 – 0.66	0.42 – 1.31

Abbreviations: mHSPC: low-volume metastatic hormone-sensitive prostate cancer patients, SGC: salivary gland cancer patients

Discussion

We performed two state-of-the-art 3D SPECT/CT dosimetry studies of [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T in a prospective setting. Therefore, we were able to compare the absorbed doses by the kidneys of each respective compound most accurately to date. We observed a ~1.5x higher median kidney absorbed dose for [^{177}Lu]Lu-PSMA-I&T (0.73 Gy/GBq) compared to [^{177}Lu]Lu-PSMA-617 (0.49 Gy/GBq). This difference was statistically significant (p=0.004). Previous preclinical studies have suggested that [^{177}Lu]Lu-PSMA-I&T resulted in a much higher (30x) kidney radiation dose compared to [^{177}Lu]Lu-PSMA-617 [8, 21]. This was recently supported by retrospective work from Schuchardt *et al*. showing a significant difference in kidney absorbed dose between these two compounds (0.77 Gy/GBq for [^{177}Lu]Lu-PSMA-617 vs. 0.92 Gy/GBq for ^{177}Lu-PSMA-I&T, P = 0.0015) [15]. However, this retrospective study is impaired by its alternating dosimetry protocol and by relying on planar imaging, which can significantly affect the accuracy of the dosimetry outcomes [22-24]. With our results, we can confirm the previous preclinical and retrospective outcomes. However, the observed differences in kidney radiation doses are considerably lower than the preclinical work suggested and more in line with the retrospective study of Schuchardt *et al*. Therefore, the risk for kidney toxicity with [^{177}Lu]Lu-PSMA-I&T may be of less concern in a real-life setting.

To date, the longest follow-up has been reported for [^{177}Lu]Lu-PSMA-617 with a median of 30.4 months. At this time, the authors did not observe a grade $\geq$3 of kidney toxicity [25]. Neither did the recently published pivotal 'VISION' trial of [^{177}Lu]Lu-PSMA-617 (median follow-up 20.9 months) [2]. However, the median follow-up in both these studies of end-stage mCRPC patients was rather short due to the poor survival in most of the patients. In addition, there is no mature data on adverse events following [^{177}Lu]Lu-PSMA-I&T yet as the results of the registration trial of [^{177}Lu]Lu-PSMA-I&T are awaited (NCT04647526) [1, 26]. Therefore, the clinical relevance of a higher radiation dose for [^{177}Lu]Lu-PSMA-I&T in the kidneys is to be determined.

The European guidelines suggests that the threshold dose of [^{177}Lu]Lu-PSMA is 40 Gy in Biological Effective Dose (BED) before kidney related toxicity occurs [5]. This threshold dose is mostly based on ^{177}Lu-DOTATATE studies and on data from external beam radiotherapy studies. We therefore urge the

need to include dosimetry in trials to adequately correlate adverse events to absorbed doses to the organs at risk. This will also pave the way for broad adoption of targeted radionuclide therapies particularly in earlier stage cancer patients and for more than a fixed amount of (4-6) cycles. After all, dosimetry of radionuclide therapies allows for personalized dosing schemes [27].

This study was limited by its two small size cohorts from two distinct malignancies with one being prostate cancer and the other SGC. However, we believe that the cancer type does not affect the kidney kinetics of [^{177}Lu]Lu-PSMA-I&T or [^{177}Lu]Lu-PSMA-617. In fact, given the higher volume of tumor burden in the SGC patients, we may even under-estimate the kidney dose in these patients compared to the low-volume mHSPC patients. However, dosimetry data from low-volume prostate cancer patients did not differ much from high volume prostate patients, thus the sink effect may have a limited impact in this setting [18, 28, 29]. Furthermore, although all 20 patients had a good kidney function, the baseline GFR was dissimilar in favor of the SGC group. The consequence of this difference is to be determined. But, a recent study showed that baseline kidney function was not predictive for kidney absorbed dose for PSMA-RLT [30].

Conclusion

This prospective five-timepoint 3D SPECT/CT dosimetry study showed that the kidney absorbed dose significantly differed between [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T, with a ~1.5x higher median kidney absorbed dose for [^{177}Lu]Lu-PSMA-I&T. Still, the difference of kidney radiation doses in the clinical setting is considerably lower than suggested by preclinical studies. Thus, the clinical relevance of the different kidney radiation doses is of less importance. Furthermore, the effect of PSMA-RLT on kidney function needs to be assessed in proper series with long-term follow-up.

Declarations

Ethics approval

All procedures performed in studies involving human participants were in accordance 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. Both studies study were approved by the Medical Review Ethics Committee Region Arnhem-Nijmegen and were registered on ClinicalTrials.gov.

Consent to participate:

Informed consent was obtained from all induvial participants included in the study.

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Data availability:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

^{177}Lu: Lutetium-177

^{68}Ga: Gallium-68

mHSPC: metastatic low-volume hormone-sensitive prostate cancer

PET: positron emission tomography
PSMA: Prostate-specific membrane antigen

PSMA-RLT: Prostate-specific membrane antigen radioligand therapy

SGC: salivary gland cancer
SPECT: Single-photon emission computed tomography
SUV: standardized uptake value

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MU, BP, MK, SP & JN. The first draft of the manuscript was written by MU & BP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors contributed to writing this manuscript. All authors read and approved of the final manuscript.

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Figures

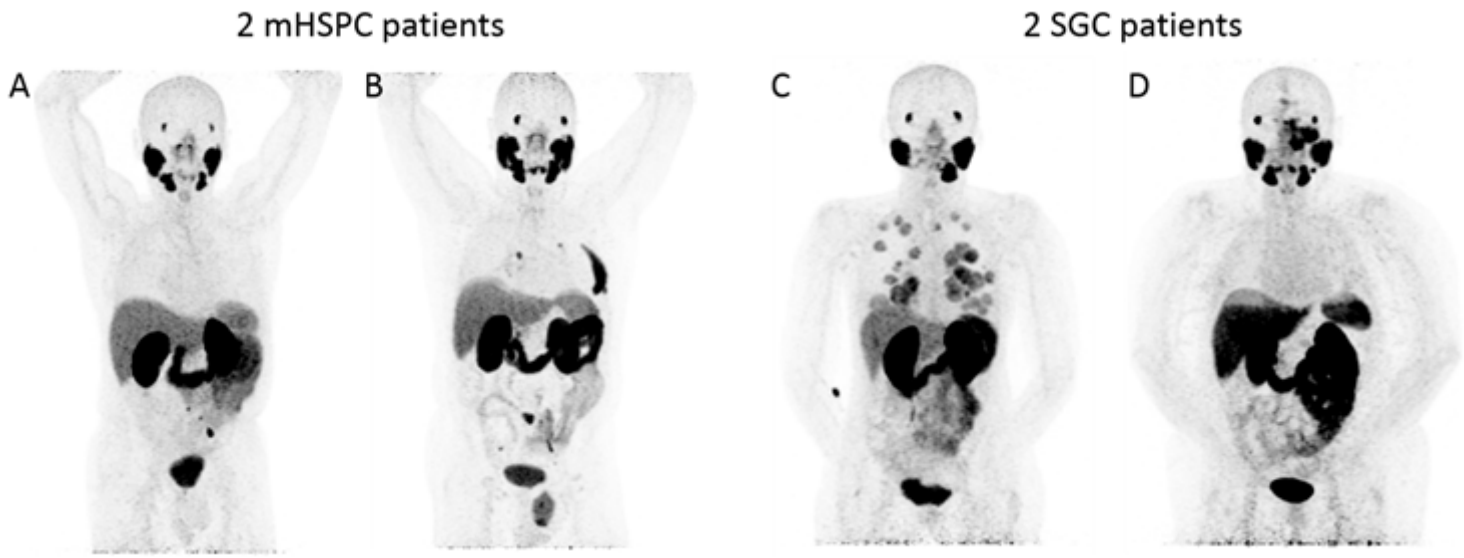

Figure 1

[Ga]Ga-PSMA-11 PET maximum intensity projections (MIP) before PSMA-RLT treatment.

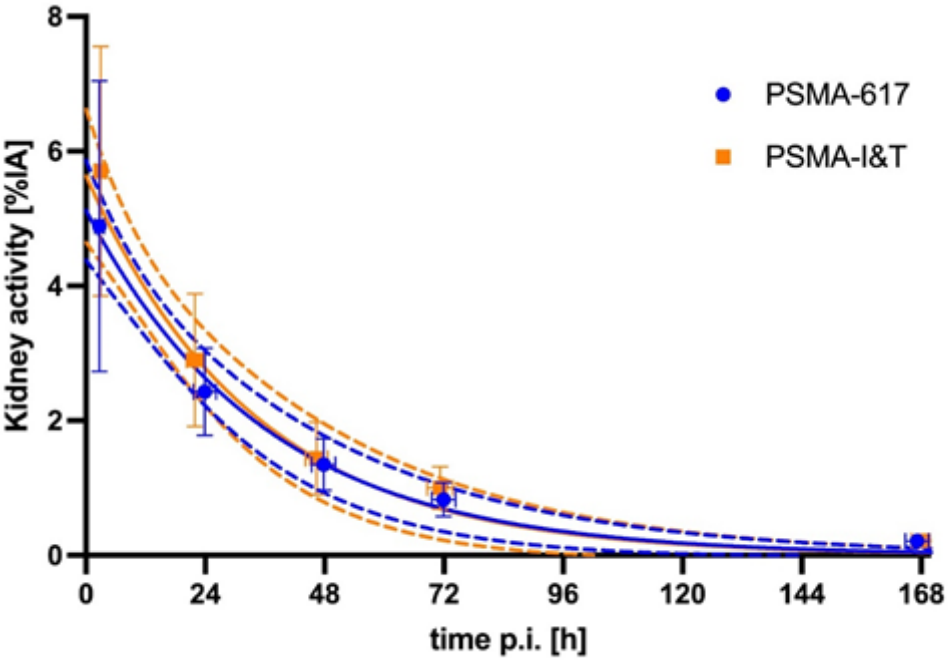

Figure 2

Kidney time-activity curves of [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T. The solid lines indicate single-exponential curve fits with their 95% confidence limits shown as dashed lines.