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Kidney doses in ^{177}Lu-based radioligand therapy in prostate cancer: Is dose estimation based on reduced dosimetry measurements feasible?

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Abstract

The radiation dose to the kidneys should be monitored in prostate cancer patients treated with radioligand therapy (RLT) targeting the prostate-specific membrane antigen (PSMA). We analyzed whether pretherapeutic kidney function is predictive of subsequent kidney dose and to what extend the cumulative kidney dose after multiple therapy cycles at the end of treatment can be predicted from a dosimetry based on the first cycle. **Methods:** Data of 59 patients treated with at least 2 cycles of ^{177}Lu-PSMA-617 (PSMA-RLT) were analyzed. Treatment (median: 6 GBq/cycle) was performed at 6-8 week intervals, accompanied by voxel-based 3D-dosimetry (measured kidney dose) with SPECT/CT on each of days 0-3 and once during days 6-9. Pretherapeutic kidney function (eGFR, MAG3-clearance) was correlated to the kidney doses. Cumulative kidney doses at the end of treatment were compared to a dose estimation based on the population-based mean kidney dose, individual first cycle kidney dose and mean kidney doses of cycles 1, 3 and 5 per administered activity. **Results:** A total of 176 PSMA-RLT cycles were performed with a median of 3 cycles per patient. The average kidney dose per administered activity of all 176 cycles was 0.67 ± 0.24 Gy/GBq (range 0.21 – 1.60). MAG3-clearance and eGFR were no reliable predictors of subsequent absorbed kidney dose and showed only small effect sizes (R^2 = 0.080 and 0.014, p = 0.039 and 0.375). All simplified estimations of cumulative kidney dose correlated significantly (p < 0.001) with measured kidney doses: Estimations based on the individual first-cycle dose were more accurate than the use of the population-based average kidney dose (R^2 = 0.853 vs. R^2 = 0.560). Dose estimation was best when the doses of cycles 3 and 5 were included as well (R^2 = 0.960). **Conclusion:** Pretherapeutic renal function was not predictive for subsequent kidney dose during therapy. Extrapolation of individual data from dosimetry of the first cycle was highly predictive for the cumulative kidney dose at the end of treatment. This is further improved by the integration of dose information from every other cycle. In any case, because of a high interindividual variance, an individual dosimetry is advisable.

Keywords:

prostate-specific membrane antigen (PSMA), radioligand therapy (RLT), lutetium-177 (^{177}Lu), renal toxicity, kidney dosimetry

Running Title:

Dose estimation for radioligand therapy

Prostate specific membrane antigen (PSMA) is frequently overexpressed in prostate cancer. Aside from imaging with positron emission tomography (PET) with ligands targeting this antigen, ^{177}Lu-based radioligand therapies (PSMA-RLT) are an emerging and promising treatment option *(1)* in patients with metastatic castration-resistant prostate cancer (mCRPC). The potential of PSMA-RLT has been demonstrated in recent phase II trials *(2-4)* and the effectiveness is currently under investigation in a multicenter phase III trial (NCT03511664).

While PSMA-RLT is generally well tolerated and shows only mild side effects, the bone marrow, salivary glands and kidneys are considered to be potentially dose-limiting organs *(5)*. In this respect, PSMA-RLT shares similarities with peptide-receptor radionuclide therapy (PRRT) for neuroendocrine tumors which also shows an overall good tolerability with renal and haematopoietic toxicity being the main side effects. As the kidney dose has been a major concern for PRRT, various protocols for nephroprotection by co-infusion of amino acids have been developed over the years *(6)*. Traditionally, a tolerance dose of 23 Gy for the kidneys is assumed in PRRT, based on external beam radiation therapy data *(7)*. As a consequence, meticulous renal dosimetry is recommended in radioligand therapies and should be thoroughly integrated into treatment protocols *(8)*.

While the kidney dose in ^{177}Lutetium-based PSMA-RLTis in a similar range when using PRRT with ^{177}Lu-DOTATATE, no protocol for nephroprotection has been established yet. Especially, there is no evidence that an amino acid co-infusion results in a lower radiation exposure to the kidneys. Based on more recent data on ^{177}Lu-based therapies, a higher renal tolerability of up to 40 Gy cumulative kidney dose is assumed in PSMA-RLT in the absence of risk factors, also taking prognostic aspects of the treated patient into account *(5)*.

In order to accurately assess kidney doses in PSMA-RLT, various procedures for dosimetry have been developed, ranging from simple planar imaging *(9)* to more complex SPECT/CT-based protocols *(10)*. In this study, the kidney dose per cycle was determined on the basis of a dosimetry protocol that includes five intratherapeutically acquired SPECT/CT. Using these data we assessed whether the cumulative kidney dose after multiple therapy cycles at the end of treatment can be reliably predicted from the dosimetry of the first therapy cycle only.

MATERIALS AND METHODS

Patients

In this retrospective analysis, data of patients with metastasized castration-resistant prostate cancer (mCRPC) that have been treated with ^{177}Lutetium-labelled PSMA-617 between 07/2015 and 07/2020 were analyzed. Patients were eligible for this analysis if two or more cycles of PSMA-radioligand therapy have been performed and complete 3D SPECT/CT dosimetry data were available, including a late SPECT/CT image from at least 6 days after injection.

Treatment eligibility and pretherapeutic examinations had been done in accordance with the recommendations of the German society of nuclear medicine *(11)*. MAG3 renal scintigraphy was used for the determination of pretherapeutic MAG3-clearance and especially the exclusion of active ureter obstruction. Patients with proven treated previous obstruction and an inconspicuous MAG3-scan were eligible for therapy.

According to the aforementioned guideline, a standard activity of 6 GBq ^{177}Lu-DOTA-PSMA-617 was applied. A reduced activity of 4 GBq was used only in cases of reduced bone marrow function or strongly impaired renal function.

The institutional review board (vote 326/18) approved this study and all subjects signed a written informed consent.

Synthesis of ^{177}Lu-DOTA-PSMA-617

The production of ^{177}Lu-DOTA-PSMA-617 was performed in compliance with GMP using an automated radiosynthesis device (Modular-Lab PharmTracer) with low bioburden single-use cassettes. The commercially available precursor (ABX, Radeberg, Germany) and reagents were prepared and sampled according to standard operation procedures. No-carrier-added $^{177}LuCl_3$ was purchased from ITM (Garching) and the cassettes were supplied by Eckert & Ziegler Eurotope GmbH. Prior to starting the synthesis, $^{177}LuCl_3$ (~ 8 GBq), ammonium acetate buffer (0.5 M, pH 5.4), 50 % ethanol and isotonic saline vials were connected to the cassette. The Sep-Pak® light C-18 cartridge was preconditioned with 4 ml 50 % ethanol and 6 ml isotonic saline. The synthesis was started by transferring $^{177}LuCl_3$ (~ 8 GBq) into the reaction vessel preloaded with 70 µg (67 nmol) DOTA-PSMA-617 and 100 µl ethanol to prevent radiolysis. The ammonium acetate buffer (700 µl) was transferred through the radioactiv vial into the reaction vessel. The radiosynthesis was carried out at 75 °C for 40 minutes in ammonium acetate buffer. The mixture was subsequently passed through the preconditioned Sep-Pak® light C-18 cartridge and washed with isotonic saline. The final product was eluted with 50 % ethanol, diluted with isotonic saline and passed through a 0.22 µm sterile membrane filter into a pre-sterilized product vial prefilled with 100 – 200 µl Ditripentat-Heyl® (DTPA, solution for injection). The quality control was conducted in adherence to European Pharmacopeia standards including filter integrity and pH test, limulus amebocyte lysate (LAL), radionuclide identity and purity test by determining the half-life and energy spectrum. Chemical and radiochemical purity (≥ 97 %) were identified by radio-high-performance liquid chromatography and the residual solvent by gas chromatography. Finally, a sample of the product formulation was tested for sterility post-release by an independent institution (Biochem) according to Ph. Eur. and USP using the direct inoculation method.

SPECT/CT imaging and dosimetry

At each therapy cycle, imaging for dosimetry was performed on days 0-3, consisting of planar whole-body scans as well as abdominal SPECT/CT (including kidneys, liver, and spleen) at 1h, 24 h, 48 h and 72 h after injection. Moreover, one late SPECT/CT was acquired on an outpatient basis in the following week on day 6, 7, 8 or 9 after injection (Figure 1).

All acquisitions were performed on a SPECT/CT (BrightView XCT, Philips Healthcare, Cleveland, OH, USA) equipped with medium energy general purpose (MEGP) collimators. Measurements were done with an energy window of ±10% around the 208keV peak. SPECT was measured with 40 projections per head on a body-contour trajectory with a 128 x 128 matrix size and 20 s acquisition duration time per projection. Attenuation correction was based on a cone-beam CT (30 mAs at 120 kV), SPECT was reconstructed iteratively with the ordered subsets expectation maximization algorithm (4 iterations and 16 subsets, post-reconstruction filter: Butterworth, cut-off: 0.4; order 1.4). Whole-body scans were performed with a velocity of 20 cm/min and an imaging matrix of 256 x 1024 to document the tracer distribution.

The SPECT/CT system was calibrated for lutetium-177 by phantom measurements with a NEMA image quality phantom using the aforementioned imaging protocol. The phantom body was filled with water and two 500ml volumes simulating kidneys were inserted, one filled with 100 MBq and one with 200 MBq lutetium-177. Calibration measurements were done 4 times every 2nd day. The resulting calibration factor was 9.9±0.4 cps/MBq. 3D dose-maps were calculated using STRATOS® which is part of the IMALYTICS Research Workstation (Philips Technology, Aachen, Germany). The software package is based on the MIRD formalism for voxel-based dose calculation by voxel-S-values *(12)*. The original SPECT images of each cycle were coregistered to CT of the last scan in STRATOS and resampled to a voxel size of 4.42x4.42x4.42 mm in accordance with STRATOS' voxel-S-value sizes. The integral of the time-activity curve for each image voxel was calculated by trapezoidal integration method until the last imaging time points, followed by an exponential tail fit using the physical half-life of lutetium-177. Due to the late time point of SPECT/CT after 6-9 days, the dose contribution of the tail fit is very low and there is only a slight difference between the use of the physical half-life or the individual effective half-life.

The software package Rover (ABX, Radeberg, Germany) was used for kidney segmentation and 3D dose-map analysis *(13)*.

In accordance with current guidelines *(5)*, pretherapeutic kidney function prior to the first cycle was assessed using the estimated glomerular filtration rate (eGFR) according to CKD-EPI *(14)* ($eGFR_{t1}$) and MAG3-Clearance derived from renal scintigraphy performed before therapy in order to rule out obstructions. eGFR was again determined approximately 2 weeks prior to the third cycle ($eGFR_{t2}$).

Statistics

For all patients and all cycles the absorbed doses by the kidneys were calculated using voxel-based 3D-dosimetry (measured kidney dose).

$eGFR_{t1}$ and MAG3-clearance were correlated with the respective kidney dose of the first cycle for every patient and, if applicable, $eGFR_{t2}$ was correlated to the third cycle dose.

In all patients, the measured cumulative kidney dose was correlated with the estimated cumulative dose, based on the population-based mean kidney dose per administered activity (Gy/GBq) observed in our cohort and on the individually calculated first-cycle kidney dose per administered activity. Moreover, in order to account for potential changes during therapy in patients receiving four or more therapy cycles, the extrapolation of the cumulative dose at the end of the treatment was done with the individual kidney dose per administered activity of every other cycle. In this case, the kidney dose of even-numbered cycles (cycles 2, 4 and 6, respectively) was estimated from the measured kidney dose of the therapy cycles immediately before (cycles 1, 3 and 5, respectively).

Correlations were based on linear regression using ANOVA for significance analysis. Paired t-tests were used for comparisons of $eGFR_{t1/t2}$ and kidney doses at different cycles. All analyses were carried out using IBM SPSS statistics software Version 27 (Armonk, NY, USA). Arithmetic mean values were calculated from the individual measurements and expressed at a precision of one standard deviation (mean ± standard deviation).

RESULTS

Patient treatment and measured kidney doses

The data of 59 patients (aged 72.8 ± 8.5, median 74.6 years) suffering from advanced mCRPC were eligible for analysis. Patients had received a median number of 3 cycles Lu-177-PSMA-617 (2 cycles: n=28; 3 cycles: n=11 4 cycles, n=16; 5 cycles, n=1; 6 cycles, n=3) at a 6-8 week intervals (total n=176 cycles). Average activity per cycle over all patients and cycles was 5.7 ± 0.8 (median 6.0) GBq of Lu-177-PSMA-617 (Cycle 1: 5.6 ± 0.9, Cycle 2: 5.8 ± 0.7, Cycle 3: 5.6 ± 1.0, Cycle 4: 6.0 ± 0.2, cycle 5: 5.9 ± 0.3 and cycle 6: 5.9 ± 0.4 GBq). The cumulative measured kidney doses in all 59 patients after PSMA-RLT ranged from 3.4 to 25.3 Gy. Average kidney dose per administered activity over all patients and cycles (n=176) was 0.67 ± 0.24 Gy/GBq (range 0.21 – 1.60). The respective kidney dose for each cycles shown in Table 1. Average kidney doses per cycle did not differ significantly (p=0.217), see Figure 2. Details on kidney doses depending on the number of cycles administered can be found for Supplemental Table 1 (total kidney dose) and Supplemental Table 2 (left and right kidney separately assessed).

Renal function and kidney dose

The $eGFR_{t1}$ ranged from 29.4 to 116.7 (76.5 ± 14.4) ml/min/1.73 m^2. According to KDIGO-criteria *(15)*, 13 patients presented with normal (KDIGO G1), 39 with mildly decreased (KDIGO G2) and 5 with a mildly to moderately decreased (KDIGO G3a) kidney function. One patient each presented with moderately to severely decreased (KDIGO G3b) and severely decreased (KDIGO G4) kidney function. MAG3-clearance ranged from 115 to 307 (202.8 ± 28.3) ml/min/1.73 m^2 and correlated poorly to $eGFR_{t1}$ (R^2 = 0.167, p = 0.002). The kidney dose per administered activity (Gy/GB) observed after the first cycle correlated neither to $eGFR_{t1}$ (R^2 = 0.014, p = 0.375) nor to MAG3-clearance (R^2 = 0.080, p = 0.039) with small effects of determination only. Similarly, the kidney dose per administered activity (Gy/GBq) of the first cycle did not correlate (R^2 < 0.001; p = 0.85) to the amount of activity used (2.09 to 6.47 GBq). In particular the 2 patients with more severely reduced kidney function did not receive higher kidney doses per GBq than other patients (0.69 Gy/GBq and 0.48 Gy/GBq for KDIGO G3b and KDIGO G4, respectively). In 31 patients, $eGFR_{t2}$ was determined and ranged from 41.5 to 95.80 (72.3 ± 17.0) ml/min/1.73 m^2. There was no correlation between $eGFR_{t2}$ and the kidney dose (Gy/GBq) of the third cycle (R^2 = 0.001, p = 0.993) and no significant change between $eGFR_{t1}$ and $eGFR_{t2}$ was observed (p = 0.96).

Predicted and measured kidney doses

In all 59 patients, correlations between the measured and estimated cumulative kidney dose at the end of treatment were significant (p < 0.001). However, the use of the population-based mean kidney dose of 0.67 Gy/GBq for the prediction of the kidney doses at the end of treatment resulted in a greater variance (R^2 = 0.560) than the use of the individual first-cycle dose per administered activity (Gy/GBq) approach (R^2 = 0.853). As expected, the approach using an individual dosimetry at every second cycle resulted in the best prediction (R^2 = 0.960), see Figure 3.

Twenty patients received 4 or more cycles. Using the same dose estimation methods in this subgroup, the use of the mean kidney dose of 0.67 Gy/GBq did not result in a meaningful

prediction (R^2 = 0.166; p = 0.074). In contrast, the individual-based dosimetry estimations still correlated significantly to the measured cumulative kidney dose (p < 0.001). The first-cycle dosimetry only showed a lower coefficient of determination than the approach using every other cycle (R^2 = 0.630 vs. R^2 = 0.947), see Figure 4.

DISCUSSION

In the present study, the average kidney dose per administered was 0.67 ± 0.24 Gy/GBq activity when performing a treatment with 6.0 GBq of Lu-177-PSMA-617. In comparison to the kidney doses reported in the EANM procedure guideline for PSMA-based RLT *(5)*, this dose average is in the upper range of the reported dose of 0.4 ± 0.2 to 0.8 ± 0.3 Gy/GBq. This finding is not surprising as we used recommended late time point measurements in the week after therapy *(16)* in order to avoid dose underestimation. In that sense, our results were consistent with the results of SPECT/CT-based dosimetry protocols also using late time-points *(5)*.

In accordance to the kidney dosimetry results reported by Okamoto et al. *(9)*, who also included the important late time points in their dose calculations, we observed an intraindividually relatively constant development of kidney dose in our patients using fixed activities. Especially in responders to therapy we did not observe postulated tumor sink effects *(17)*, e.g. a reciprocal increase in intraindividual kidney dose per cycle due to decreasing tumor burden.

Using a state-of-the-art multi SPECT/CT 3D dosimetry approach, the high coefficients of determination observed in cumulative kidney dose based on personalized dosimetry show that a linear extrapolation of the individual kidney dose development within the bounds of a rigid treatment setting (i.e. activity and time intervals) is feasible. Our data suggest that an individual dosimetry of the first cycle allows a sufficient prediction of the cumulated kidney dose at the end of treatment. Obviously, we see a higher coefficient of determination for the estimated cumulative kidney dose when also including dosimetry data from cycles 3 and 5 (if applicable). Comparable considerations on the prediction of kidney dose have been reported for PRRT in neuroendocrine tumors based on the dosimetry of the first two cycles *(18)*. In addition to these dose prediction approaches, measures such as the reduction of the number of CT- or SPECT/CT-acquisitions per cycle *(18,19)* have been suggested in order to simplify often elaborated dosimetry protocols *(20)*. These simplifications would not only free scanner and staff capacities at the nuclear medicine facility but also improve patient comfort *(21,22)*. Considering this, our approach of a thorough dosimetry of the first cycle followed by extrapolation appears to be a viable option, again provided that also crucial late measurement time points are included in such protocols to avoid potential underestimation *(16,23)*. However, especially when aiming at a more streamlined dosimetry or larger dosimetry intervals, the high interindividual variation of the resulting kidney dose after PSMA RLT (0.28 to 1.29 Gy/GBq at the first cycle in our cohort), likewise observed in PRRT *(23,24)*, must be taken into account. The poor cumulative dose estimation using a population-based mean kidney dose only, especially if patients received 4 or more cycles, shows that a reliable individual dosimetry is essential. Accordingly, the usage of an average kidney dose values from literature for the prediction should be refrained from.

Our results showed that the pretherapeutic renal function was not predictive for subsequent kidney dose during therapy. In our cohort, 57/59 patients had normal or only slightly impaired renal function prior to PSMA-RLT. Even taking the two-patients with more severely impaired kidney function KDIGO G3b and G4 into account, we observed neither an association between pretherapeutic kidney function ($eGFR_{t1}$) and the first-cycle kidney dose, nor between kidney function after two cycles ($eGFR_{t2}$) and kidney dose at the third therapy cycle. Although the association between the kidney dose of the first cycle and MAG3-clearance was significant, the

associated effect size was very small (R^2 = 0.062). These observations imply that kidney function alone is not sufficient for the prediction of the resulting kidney dose.

While the role of potential risk factors for kidney damage *(25)* such as age, arterial hypertension, or previous renal impairment still remains to be determined, retrospective PSMA-RLT series have reported mild renal toxicity grades 1/2 only *(25,26)*. Even a safe administration of PSMA-RLT also in patients with only a single kidney is possible *(27)*. These observations are confirmed by the updated analysis of the prospective phase II LuPSMA trial indicating that approximately 4 cycles of RLT are well tolerated and renal impairment has to be expected only after a higher number of cycles *(3)*. Similarly, nephrotoxicity was also not a major adverse event in the recently published phase II TheraP trial *(4)*. These observations on renal tolerance in Lu-177-PSMA RLT are partly comparable to data on renal tolerance of Lu-177-DOTATATE, as the phase III Netter-1 trial did not show higher grade 3/4 renal toxicity during the median 14-month follow-up *(28)*. Even secondary salvage PRRT is sufficiently tolerated by the kidneys whereas high-grade hematotoxicity is a more relevant issue *(29)*. In this aspect, hematotoxicity may also be a more relevant side effect in patients with renal impairment as a slower renal excretion might result in a longer exposure of the bone marrow due to circulating radioligand.

Although long-term data on renal safety of PSMA RLT are still warranted, observations from PRRT suggest that the development of renal impairment is gradual over many years *(30)*. Considering the often poorer prognosis of advanced mCRPC compared to NET-disease, the individual risk to actually experience late kidney damage also has to be taken critically into account *(5)*. Additionally, the risk of premature of discontinuation of therapy in PSMA-RLT due to disease progression and development of resistance to therapy must be heeded. Only one third of our patients received 4 or more therapy cycles and as a consequence, only 6 patients had a cumulated kidney doses that came close or even slightly surpassed the aforementioned conservative threshold of 23 Gy. Thus, in our cohort with a limited number of patients, kidney dose was not a reason for discontinuation of therapy.

CONCLUSION

Using a current standard PSMA RLT treatment protocol, resulting kidney doses were independent from pretherapeutic kidney function.

Due to the observed almost linear correlation between treatment activity and the cumulative kidney dose in individual patients, a prediction of the cumulative kidney dose with dosimetry results from the first cycle only, seems to be feasible. Based on our findings for patients with more than 4 therapy cycles, we recommend the performance of dedicated dosimetry during every other therapy cycle, which offers a good compromise between effort, patient comfort and accuracy of the estimated cumulative kidney dose.

Disclosure from all authors: MM, TR, FK, UN, EY, TM, AO, PTM and JR have no conflicts of interest. 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.

Key points

Question: Is an accurate prediction of kidney dose in ^{177}Lu-PSMA radioligand therapy in prostate cancer patients feasible with reduced SPECT/CT measurements for dosimetry?

Pertinent findings: A simplification of intratherapeutic imaging protocols by performing dosimetry only at the first or every other therapy cycle is feasible.

Implications for patient care: A reduction of dosimetry measurements improve patient comfort and is freeing scanner and staff capacities but an individual kidney dosimetry is essential for accurate dose estimation.

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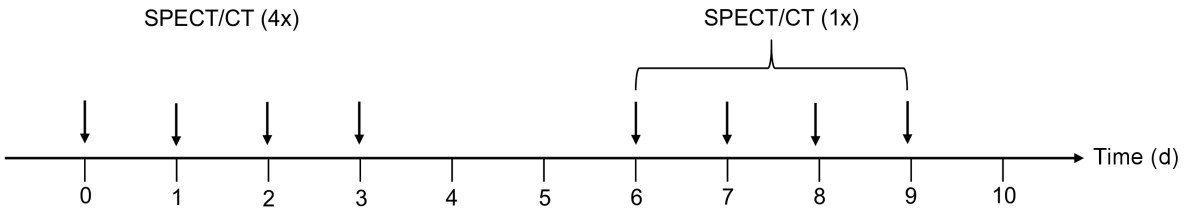


Figure 1. Schematic overview of SPECT/CT measurements performed on day 0-3 (on an inpatient base) and on day 6, 7, 8 or 9 (on an outpatient base).

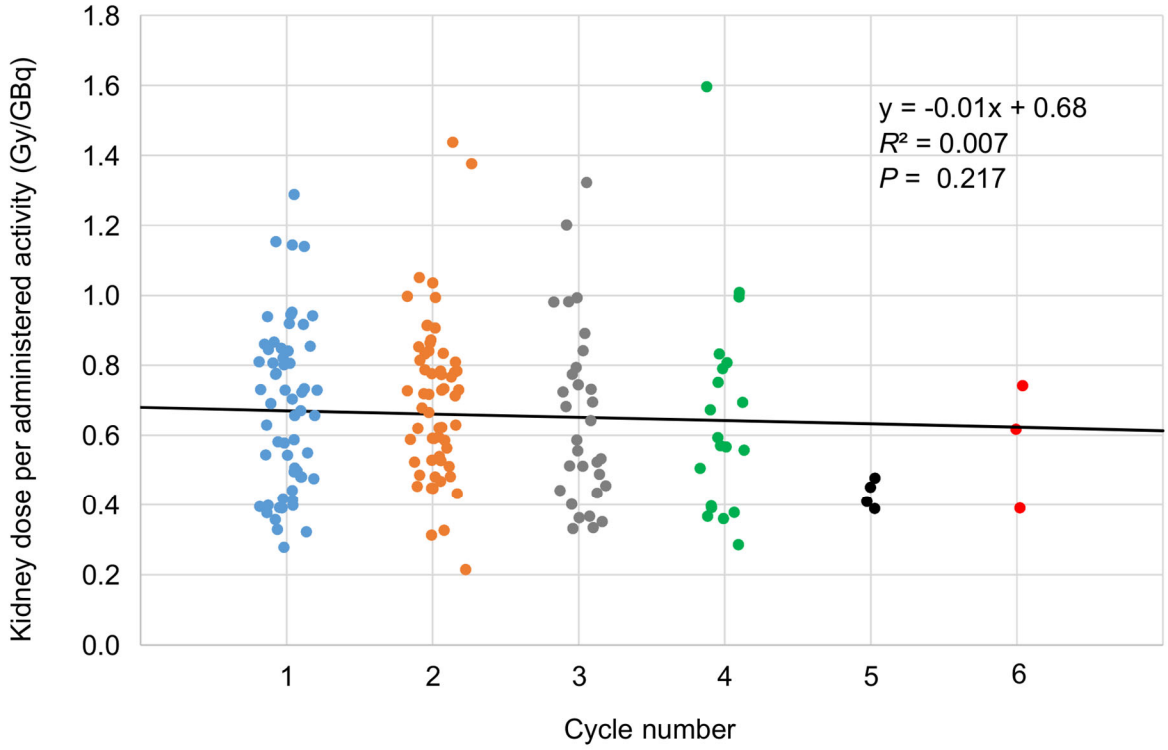


Figure 2. Comparing kidney dose per administered activity (Gy/GBq) distribution per cycle (59 patients), no significant changes in all 6 cycles were observed (p = 0.217).

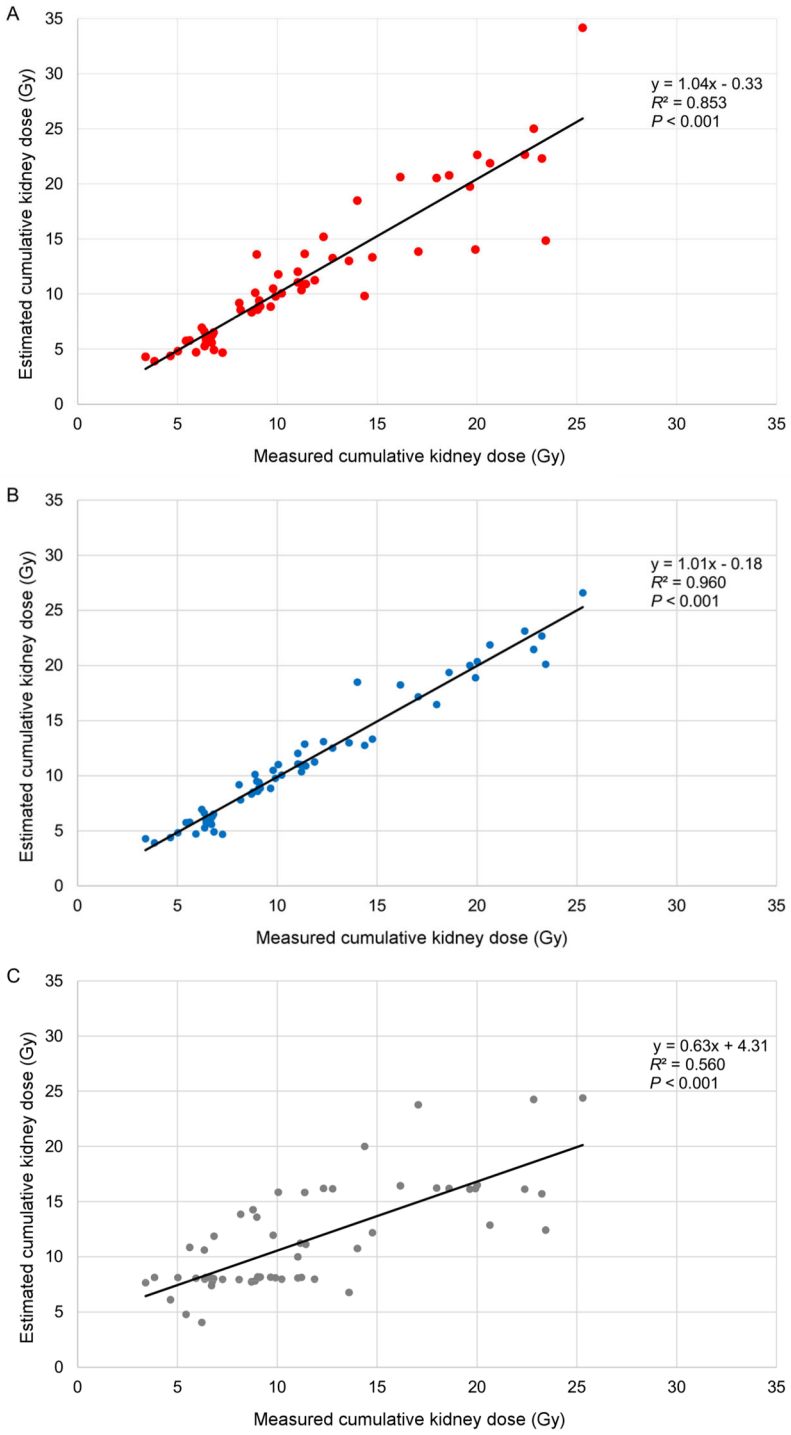


Figure 3. Correlations of estimated and measured cumulative kidney dose in all 59 patients based on three models. The good correlation and coefficient of determination seen when extrapolation is done using the individual dose per administered activity from first-cycle dosimetry (A) can be further improved when data of cycle 3 and 5 are also taken into account (B). In contrast the poorest coefficient of determination was observed using a population-based average kidney dose only (C), in which the estimation resulted in a systematic dose underestimation (see slopes).

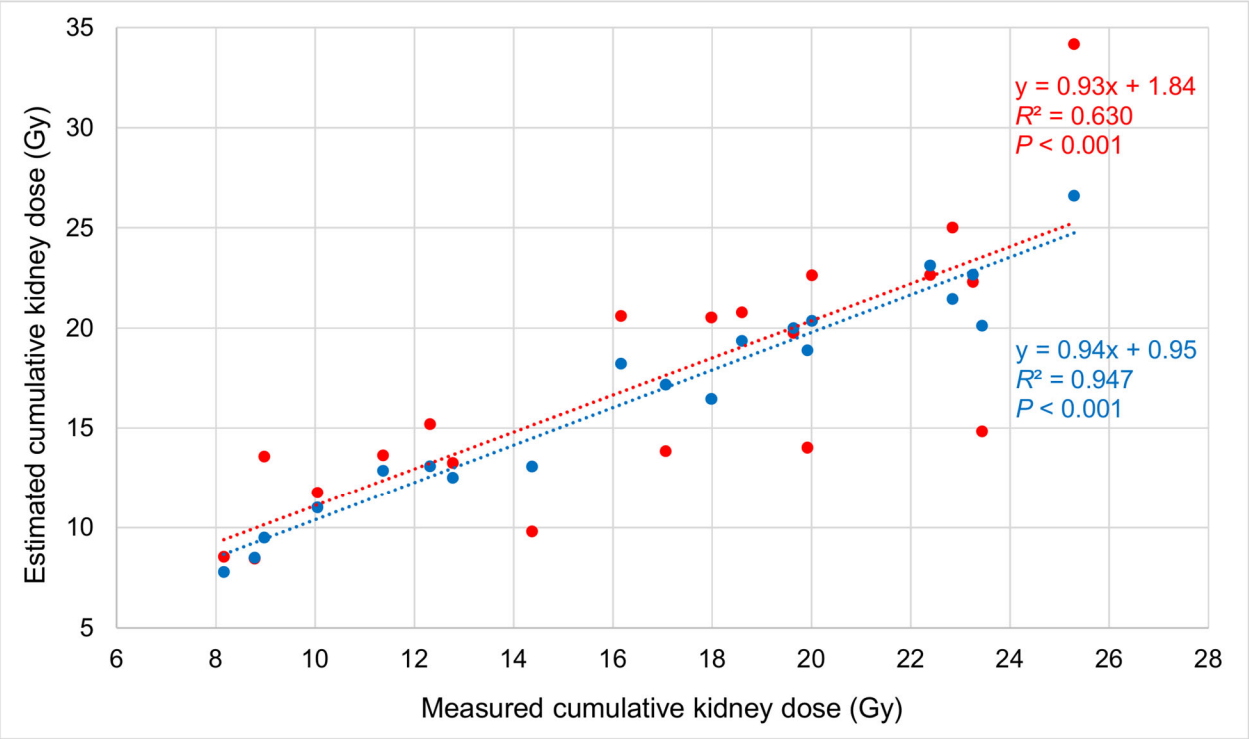


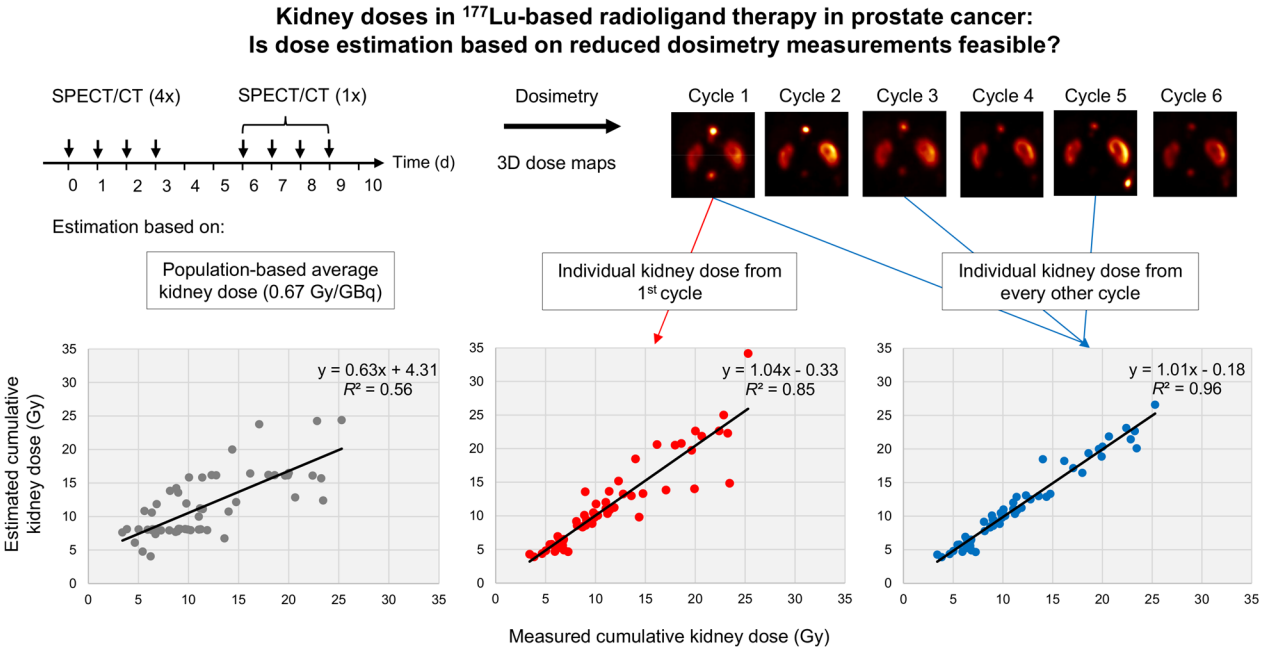
Figure 4. Correlation of estimated and measured cumulative kidney dose in 20 patients receiving 4 and more therapy cycles based on dosimetry of cycle 1 only (red) and cycle 1, 3 and 5 (blue) The use of an individual average kidney dose from every second cycle greatly improves the associated coefficient of determination.

Table 1: Kidney dose at each cycle

kidney dose per administered activity (Gy/GBq)						
	cycle 1	**cycle 2**	**cycle 3**	**cycle 4**	**cycle 5**	**cycle 6**
# of patients	**59**	**59**	**31**	**20**	**4**	**3**
Mean	**0.68**	**0.70**	**0.65**	**0.66**	**0.43**	**0.58**
SD	**0.24**	**0.23**	**0.26**	**0.31**	**0.04**	**0.18**
Min	**0.28**	**0.21**	**0.33**	**0.29**	**0.39**	**0.39**
Max	**1.29**	**1.44**	**1.32**	**1.60**	**0.48**	**0.74**

Legend: SD: standard deviation, Min: minimum, Max: maximum

Graphical Abstract



Supplemental Table 1: Kidney dose at each cycle for subgroups with a different number of therapy cycles

kidney dose per administered activity (Gy/GBq)							
subgroup with 6 cycles (3 patients)							
	cycle 1	**cycle 2**	**cycle 3**	**cycle 4**	**cycle 5**	**cycle 6**	**% Delta**
Mean	**0.67**	**0.67**	**0.70**	**0.55**	**0.42**	**0.58**	**-11**
SD	**0.27**	**0.18**	**0.15**	**0.15**	**0.05**	**0.18**	**10**
Min	**0.39**	**0.48**	**0.53**	**0.39**	**0.39**	**0.39**	**-21**
Max	**0.94**	**0.84**	**0.79**	**0.67**	**0.48**	**0.74**	**0**
subgroup with 4 cycles (16 patients)							
	cycle 1	**cycle 2**	**cycle 3**	**cycle 4**	**% Delta**		
Mean	**0.71**	**0.71**	**0.67**	**0.68**	**-1**		
SD	**0.19**	**0.26**	**0.29**	**0.34**	**37**		
Min	**0.40**	**0.45**	**0.33**	**0.29**	**-44**		
Max	**0.95**	**1.38**	**1.32**	**1.60**	**99**		
subgroup with 3 cycles (11 patients)							
	cycle 1	**cycle 2**	**cycle 3**	**% Delta**			
Mean	**0.66**	**0.64**	**0.62**	**-4**			
SD	**0.29**	**0.18**	**0.26**	**22**			
Min	**0.28**	**0.33**	**0.33**	**-40**			
Max	**1.15**	**0.91**	**1.20**	**32**			
subgroup with 2 cycles (28 patients)							
	cycle 1	**cycle 2**	**% Delta**				
Mean	**0.68**	**0.73**	**12**				
SD	**0.24**	**0.23**	**29**				
Min	**0.32**	**0.21**	**-43**				
Max	**1.29**	**1.44**	**111**				

Legend: SD: standard deviation, Min: minimum, Max: maximum, % Delta: mean change between first and last therapy cycle

Supplemental Table 2: Kidney dose at each cycle, separated for left and right kidney

kidney dose per administered activity (Gy/GBq)						
	cycle 1	**cycle 2**	**cycle 3**	**cycle 4**	**cycle 5**	**cycle 6**
# of patients	**59**	**59**	**31**	**20**	**4**	**3**
right kidney						
Mean	**0.67**	**0.70**	**0.62**	**0.64**	**0.43**	**0.59**
SD	**0.25**	**0.24**	**0.29**	**0.32**	**0.06**	**0.19**
Min	**0.13**	**0.21**	**0.17**	**0.17**	**0.36**	**0.40**
Max	**1.34**	**1.44**	**1.32**	**1.60**	**0.50**	**0.79**
left kidney						
Mean	**0.68**	**0.69**	**0.64**	**0.63**	**0.43**	**0.57**
SD	**0.25**	**0.23**	**0.27**	**0.22**	**0.02**	**0.17**
Min	**0.26**	**0.20**	**0.17**	**0.17**	**0.41**	**0.38**
Max	**1.31**	**1.43**	**1.19**	**0.98**	**0.46**	**0.70**

Legend: SD: standard deviation, Min: minimum, Max: maximum