

Investigating renal tissue responses to radiopharmaceutical therapy using multiparametric MRI

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Abstract

Objectives

Renal toxicity is a recognized potential adverse effect of radiopharmaceutical therapy (RPT). While ^{177}Lu -based therapies are generally well tolerated, subtle therapy-related renal changes remain insufficiently characterized. This study investigated longitudinal renal alterations during ^{177}Lu -based RPT using multiparametric magnetic resonance imaging (mpMRI) and evaluated its potential for renal monitoring.

Methods

Twenty-three patients undergoing RPT with either [^{177}Lu]Lu-DOTATATE (n = 14) or [^{177}Lu]Lu-PSMA (n = 9) underwent renal mpMRI examinations before and during therapy with up to four treatment cycles. Imaging included arterial spin labeling, diffusion-weighted imaging with intravoxel incoherent motion analysis, blood oxygenation level-dependent imaging, T1 mapping, and volumetry. Renal scintigraphy, estimated glomerular filtration rate (eGFR), and absorbed renal radiation dose were assessed longitudinally.

Results

No significant decline in eGFR was observed during RPT after exclusion of two patients who developed urinary tract obstruction (p = 0.19). Longitudinal analysis revealed significant temporal changes in T1 values (p = 0.008) and perfusion fraction of IVIM (p = 0.005), as well as a modest decrease in the corticomedullary BOLD ratio (p = 0.020). No significant longitudinal changes were detected for other MRI or scintigraphic parameters. Absorbed renal radiation dose was not associated with changes in MRI-derived biomarkers, eGFR, or renal scintigraphy (all p > 0.05). Patients with urinary obstruction demonstrated distinct MRI abnormalities, including reduced renal blood flow (RBF) and altered BOLD metrics.

Conclusions

No clinically relevant renal functional deterioration or major imaging abnormalities were detected during contemporary ^{177}Lu -based RPT. Subtle longitudinal T1 increases may reflect mild structural tissue remodeling without measurable functional consequences. Renal mpMRI is feasible for non-invasive monitoring and may provide complementary information beyond conventional renal function assessment.

Trial registration, DRKS, DRKS00018966, registered 10 October 2019; <https://www.drks.de/search/de/results>

Key points

- Can multiparametric MRI detect early renal tissue changes during Lu-based radiopharmaceutical therapy beyond conventional measures of renal function and scintigraphy?
- No clinically relevant renal functional deterioration was detected. Multiparametric MRI revealed only subtle longitudinal T1 changes, without associations with absorbed radiation dose or renal function.
- Multiparametric renal MRI enables non-invasive assessment of renal tissue characteristics and may complement conventional renal monitoring by detecting subtle structural changes during radiopharmaceutical therapy, potentially improving the evaluation of treatment-related renal effects.

Introduction

Radiopharmaceutical therapy (RPT) has emerged as a highly effective and increasingly established treatment modality in oncology over the past decade, particularly for advanced gastroenteropancreatic neuroendocrine tumors(1, 2) and metastatic

castration-resistant prostate cancer (3, 4), demonstrating significant improvements in progression-free survival and patient outcomes in large randomized trials (5, 6).

Despite its targeted nature, RPT is associated with potential off-target toxicity due to physiological tracer uptake and clearance pathways. However, the actual clinical relevance of radiation-associated renal tissue changes remains controversial. While several studies reported measurable declines in renal function and occasional clinically relevant nephrotoxicity (7–12), others demonstrated largely stable kidney function (13–19) even after repeated treatment cycles (20, 21). Recent evidence suggests that RPT may also be feasible in selected patients with pre-existing renal impairment (22–24). Many published cohorts comprise relatively short follow-up intervals, potentially underestimating delayed renal effects that may only become apparent years after therapy completion (25). Furthermore, the interpretation of renal function decline is complicated by confounding factors including aging, hypertension, diabetes, oncologic progression, dehydration, obstructive uropathy, or concomitant nephrotoxic medication (26).

Currently available diagnostic methods for renal assessment have important limitations. Serum creatinine and glomerular filtration rate (GFR) provide only global and relatively insensitive measures of renal function, often failing to detect early or subtle changes (27, 26). Similarly, renal scintigraphy provides valuable functional information, particularly regarding split renal function and tracer kinetics, but it is not designed to capture detailed structural or microstructural alterations of renal tissue (28, 29). As a result, it remains unclear whether clinically relevant nephrotoxicity associated with RPT is adequately captured by these conventional methods or potentially underestimated.

Multiparametric magnetic resonance imaging (mpMRI) has emerged as a promising non-invasive tool for the comprehensive assessment of renal structure and function. By combining multiple quantitative and functional imaging techniques - such as diffusion-weighted imaging (DWI), imaging of oxygenation with blood-oxygenation-level dependent (BOLD) imaging, perfusion imaging with arterial spin labeling (ASL) and T1/T2 mapping - mpMRI enables a detailed evaluation of renal tissue characteristics without the use of ionizing radiation and without the need for contrast agents (30). Importantly, mpMRI has already demonstrated high sensitivity for detecting early renal changes in various kidney diseases, including chronic kidney disease (31), diabetic nephropathy (32, 33), and renal fibrosis (34), with high predictive value compared to conventional functional parameters (35–37).

The aim of this study was to investigate longitudinal renal structural and functional changes during RPT using multiparametric MRI. In addition, we evaluated the relationship between mpMRI-derived biomarkers, conventional measures of renal function (eGFR and renal scintigraphy), and cumulative renal radiation dose to assess the potential value of mpMRI for renal monitoring during RPT.

Methods

Study design and participants

This prospective single-center study was approved by the local institutional review board and all participants provided written informed consent prior to enrolment.

Between April 2021 and December 2022, twenty-four adult patients scheduled to undergo RPT were consecutively recruited. Inclusion criteria comprised planned RPT with either [¹⁷⁷Lu]Lu-DOTATATE, [¹⁷⁷Lu]Lu-HA-DOTATATE, [¹⁷⁷Lu]Lu-PSMA-617 or [¹⁷⁷Lu]Lu-PSMA-I&T. Exclusion criteria were known pre-existing renal disease and standard contraindications to MRI. All enrolled participants underwent renal mpMRI at baseline and during each treatment cycle.

Radiopharmaceutical therapy

The indication for RPT was determined by a multidisciplinary tumor board in accordance with current clinical guidelines. Available therapies at our hospital were [¹⁷⁷Lu]Lu-DOTATATE, [¹⁷⁷Lu]Lu-HA-DOTATATE and [¹⁷⁷Lu]Lu-PSMA-I&T. Since no

significant differences have been reported for [^{177}Lu]Lu-DOTATATE and [^{177}Lu]Lu-HA-DOTATATE regarding radiation dose (38–40), we used the unified term [^{177}Lu]Lu-DOTATATE and [^{177}Lu]Lu-PSMA.

Eligibility for treatment required adequate baseline renal function and renal scintigraphy. Standard amino acid infusions were routinely administered for nephroprotection and sufficient hydration was ensured throughout hospitalization. Therapy cycles were typically performed at intervals of approximately 8 weeks, with up to four cycles planned.

Renal scintigraphy

Renal scintigraphy was performed using technetium-99m mercaptoacetyl-triglycine ($^{99\text{m}}\text{Tc}$ -MAG3) to assess renal function at baseline and to monitor potential therapy-related changes over time. The examination was conducted in line with the SNMMI/EANM joint guideline (41). Patients received a bolus injection of approximately 100 MBq and the total kidney function was estimated by calculating the tubular extraction rate of $^{99\text{m}}\text{Tc}$ -MAG3 (TER) from single blood samples using the method of Bubeck (42). Split renal function was assessed using background-corrected regions of interest placed over both kidneys and comparing the radioactivity count integrals measured between appr. 60–120 seconds per injection.

Clinical renal function assessment

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation and routinely assessed as part of standard clinical care during the clinical stay prior to each RPT cycle. In addition, follow-up eGFR measurements were obtained 12 months after the final therapy cycle to monitor longitudinal changes in renal function.

Nephrotoxic observations were graded following the common terminology criteria for adverse events (CTCAE v6) provided by the National Cancer Institute to ensure consistency and comparability with other studies.

The eGFR was additionally analyzed as percentage change from baseline and categorized into three groups: stable renal function, eGFR decline $\geq 10\%$ to $< 30\%$, and eGFR decline $\geq 30\%$.

Renal Dosimetry during RPT

Quantitative image reconstruction was performed using the Volumetrix Suite integrated into the Xeleris workstation (GE Healthcare). Following reconstruction, the kidneys were segmented for quantitative evaluation. Voxel-based metrics, including the maximum, mean, and standard deviation of the activity concentration, as well as the total activity and organ volume, were derived from the images. The resulting quantitative data were imported into OLINDA (Hermes Medical Solutions) for absorbed dose estimation. A bi-exponential kinetic model was applied, with a near-zero activity at time zero to represent the tracer distribution phase prior to the first measurement. The fit parameters were iteratively optimized until physiologically plausible and stable effective half-lives were obtained. The total kidney absorbed dose was calculated as the weighted mean of the individual kidney dose.

Multiparametric renal MRI

Renal mpMRI was performed in all patients during the clinical stay at baseline before the first therapy cycle (time point (TP)1) and repeated before subsequent therapy cycles (TP2–4) using a standardized protocol as described in detail in our prior publication (43). Image acquisition was performed on a 3T MRI system (MAGNETOM Prisma^{fit}, Siemens Healthcare AG, Erlangen, Germany).

In brief, the protocol comprised structural and functional MRI techniques including arterial spin labeling (ASL) for renal perfusion assessment, diffusion-weighted imaging (DWI) with intravoxel incoherent motion (IVIM) analysis, blood oxygenation

level-dependent (BOLD) imaging for tissue oxygenation, T1 relaxation time for tissue characterization and volumetric imaging for morphological assessment.

Post-processing included motion correction, quantitative map generation (renal blood flow (RBF), apparent diffusion coefficient (ADC), perfusion fraction (FP), T1, T2*), and segmentation-based image analysis as previously reported (43, 44). Regions of interest for the whole kidney excluding the pelvis, cortex and medulla were manually delineated for each kidney on anatomical images and transferred to parametric maps. Whole-kidney measurements were extracted, and corticomedullary ratios (CMR) were calculated where applicable. Bilateral values were averaged for patient-level analyses unless otherwise specified.

Statistical analysis

Statistical analyses were performed using R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 11.0.1 (GraphPad Software, Boston, MA, USA). All tests were two-sided, and p-values < 0.05 were considered statistically significant. For MRI-based analyses, kidneys were evaluated separately where applicable.

Longitudinal changes in imaging and renal functional parameters were analyzed using linear mixed-effects models including subject-specific random intercepts to account for repeated measurements. Fixed effects included measurement time and relevant clinical subgroup variables. Associations between longitudinal changes in imaging biomarkers and renal function were evaluated by correlating individual parameter slopes derived from mixed-effects models. For exploratory analyses involving multiple testing, p-values were adjusted using the Benjamini–Hochberg false discovery rate procedure.

Patients were additionally stratified according to longitudinal eGFR decline into groups with stable renal function, eGFR decline of 10–30%, and eGFR decline > 30%. Group differences in MRI-derived parameters were assessed using mixed-effects models with Bonferroni-adjusted post hoc comparisons.

Exploratory receiver operating characteristic (ROC) analyses were performed to evaluate the ability of baseline MRI parameters, longitudinal imaging slopes, and cumulative radiation dose to identify patients with subsequent eGFR decline of 10–30%. Predictive performance was quantified by the area under the curve (AUC) with corresponding 95% confidence intervals.

Results

Patient characteristics

A total of 24 patients were recruited for MR-imaging. Figure 1 summarizes patient enrollment, exclusion, and follow-up throughout the study period.

All 23 patients underwent at least one MRI examination. Complete longitudinal MRI follow-up with four scans was available in seven patients (30%). Five patients (22%) completed three MRI examinations, eight patients (35%) completed two examinations, and three patients (13%) had only baseline MRI data available. Patient characteristics are described in Table 1.

Table 1
Patient characteristics (n = 23)

Characteristic	Value
Number of included patients	23
Age, years (mean $\pm$ SD)	70.9 $\pm$ 9
Female sex, n (%)	6 (26)
BMI (mean $\pm$ SD)	26.0 $\pm$ 4.3 kg/m ²
Therapy: [¹⁷⁷ Lu]Lu-DOTATATE, n (%)	14 (61)
Therapy: [¹⁷⁷ Lu]Lu-PSMA, n (%)	9 (39)
Radiation dose per kidney, mGy (mean $\pm$ SD)	3629.96 $\pm$ 1579.75
Baseline eGFR (T0), mL/min/1.73 m ² (mean $\pm$ SD)	92.6 $\pm$ 25.1
Study discontinuation, n (%)	16 (70)
– Progressive disease	7 (30)
– Anemia	3 (13)
– Psychological distress	2 (9)
– Stroke	1 (4)
Outcome, n (%)	13 (56)
Progressive disease	5 (22)
Good therapy response	4 (18)
Stable disease	1 (4)
Mixed response	

Average baseline eGFR before the first therapy cycle was 92.6 $\pm$ 25.1 mL/min/1.73 m². Two patients showed eGFR below 60 mL/min/1.73 m² at TP0, but renal function was considered sufficient for RPT by the multidisciplinary tumor board. Two patients developed unilateral urinary outflow obstruction identified by renal scintigraphy during therapy and received a double-J ureteral stent.

Six patients (26%) had preexisting hypertension. One patient (4%), who also developed urinary obstruction later, had pre-existing non-insulin-dependent diabetes. No patient received additional nephrotoxic medication during therapy and follow-up.

Baseline associations between MR parameters and clinical variables

Age showed significant negative correlations with BMI ($\rho = -0.52$, $p = 0.011$), body height ($\rho = -0.57$, $p = 0.004$), and renal volume ($\rho = -0.43$, $p = 0.042$). BMI correlated positively with body height ($\rho = 0.59$, $p = 0.003$) and renal volume ($\rho = 0.47$, $p = 0.024$). The strongest association was observed between body height and renal volume ($\rho = 0.60$, $p = 0.003$).

Among functional imaging parameters, TER correlated positively with FP ($\rho = 0.49$, $p = 0.041$). In addition, ADC demonstrated a moderate positive correlation with BOLD ($\rho = 0.50$, $p = 0.016$), while BOLD correlated positively with CMR of RBF ($\rho = 0.42$, $p = 0.044$). No significant correlations were observed for eGFR, RBF, T1 or most remaining CMR-derived parameters (see Fig. 3A)

Comparison between applied RPTs demonstrated that patients with [¹⁷⁷Lu]Lu-PSMA had a higher BMI compared with patients with [¹⁷⁷Lu]Lu-DOTATATE ($p = 0.041$). No significant differences were observed between different RPTs for renal function (eGFR, $p = 0.063$) or any MRI-derived renal parameters (all $p > 0.3$). Right-to-left RBF ratio did not correlate with the split renal function assessed by scintigraphy (Spearman $\rho = 0.16$, $p = 0.50$).

Longitudinal change in renal function

Longitudinal change in eGFR

Excluding the two patients with one-sided urinary obstruction during therapy, no change in grading according to CTCAE indicating a nephrotoxic event could be observed. One-year follow-up depicted either stable renal function grading or even increased eGFR with change from G2 to G1 in 3 patients (13%). A decrease in eGFR between 10 and 30% from baseline was observed in five patients and a $\geq 30\%$ decrease in one patient. Among the two patients with pre-existing reduced renal function, one developed urinary obstruction and the other showed an 11% decrease in eGFR over time (see Fig. 2A).

No significant change in eGFR across time points ($F(1.41, 21.09) = 1.80, p = 0.19$) could be observed (see Fig. 2B). There was no significant difference in longitudinal change between RPTs ($p = 0.17$)

Longitudinal changes in MR parameters

A significant global effect of time was found for T1 ($p = 0.0083$) and FP ($p = 0.0047$) (see Fig. 2D). CMR of BOLD showed a significant linear decrease over time ($\beta \approx -5.25$ per time unit, $p = 0.020$) (Fig. 2D). Other parameters as well as their CMR did not demonstrate significant changes over time (all $p > 0.05$). There was no significant difference in longitudinal changes between RPTs ($p = 0.21$).

Correlation analysis between longitudinal renal function parameters

Spearman correlation analysis of patient-specific longitudinal slopes showed positive correlations between ADC and BOLD ($\rho = 0.57, p = 0.004$), ADC and CMR-BOLD ($\rho = 0.49, p = 0.018$), BOLD and renal volume ($\rho = 0.48, p = 0.019$), eGFR and RBF ($\rho = 0.42, p = 0.046$), and CMR-ADC and T1 ($\rho = 0.42, p = 0.047$). However, none of these associations remained significant after false discovery rate correction, indicating that these findings should be considered exploratory. Also, no longitudinal association was observed between the temporal changes in the MRI-derived RBF ratio and split renal function derived from renal scintigraphy ($\rho = -0.13, p = 0.65, n = 14$) (see Fig. 3B).

Longitudinal analysis of renal outcome groups

Pairwise group comparisons revealed significantly lower RBF values in patients with urinary obstruction compared with stable patients ($\beta = -40.7, p = 0.0039$) (Fig. 4A). In addition, BOLD values differed significantly between urinary obstruction and stable patients ($p = 0.00014$) (Fig. 4B). Significant differences were also found for CMR of BOLD between patients with urinary obstruction and eGFR decline $\geq 30\%$ ($p = 0.0006$), for CMR of T1 between urinary obstruction and patients with eGFR decline ≥ 10 – $<30\%$ ($p = 0.0015$) and for CMR of FP between urinary obstruction and eGFR decline $\geq 30\%$ ($p = 0.025$) (see Fig. 4C-E), although this association did not remain significant after Bonferroni correction. Renal scintigraphy was not included in the analysis due to a high proportion of missing data.

Figure 5 illustrates representative longitudinal imaging changes in a patient who developed unilateral urinary tract obstruction during RPT.

Effect of radiation dose on renal function

No significant difference in cumulative radiation dose was found between different outcome groups (all $p > 0.05$). Overall, no significant correlations were observed between cumulative radiation dose and the longitudinal slopes of MRI-derived parameters or renal function measures with eGFR and renal scintigraphy (all $p > 0.05$) (see Fig. 6A-D).

Prediction of eGFR decline ≥ 10 up to $< 30\%$

The highest discriminative ability for predicting renal function decline ≥ 10 up to $< 30\%$ from baseline MR values (TP1) was observed for RBF, with an AUC of 0.73 (95% CI 0.51–0.96, $p = 0.10$), followed by BOLD with an AUC of 0.69 (95% CI 0.45–0.93, $p = 0.19$). The remaining MR parameters demonstrated only low to moderate AUC values ranging from 0.52 to 0.61. Similarly,

the CMR-derived parameters as well as eGFR (AUC 0.58) and TER (AUC 0.61) demonstrated limited predictive performance (Fig. 7A).

Exploratory ROC analyses based on longitudinal parameter slopes (TP1-4) demonstrated the highest discriminatory performance for FP slope (AUC 0.79, 95% CI 0.56–1.00, $p = 0.056$), followed by RBF slope (AUC 0.69, 95% CI 0.44–0.95, $p = 0.190$). Other parameters showed limited predictive performance with lower AUC values. Also, cumulative radiation dose demonstrated moderate discriminatory performance for identifying patients with subsequent renal function decline (AUC 0.75, 95% CI 0.50–1.00, $p = 0.146$) (Fig. 7B).

Discussion

In the present pilot study, 23 patients underwent for RPT following multidisciplinary tumor board recommendation. Two patients had pre-existing moderate renal impairment prior to RPT initiation, corresponding to an eGFR between 30 and 60 mL/min/1.73 m². During therapy cycles, no patient had to delay or discontinue RPT because of renal function deterioration. Two patients were diagnosed with one-sided urinary obstruction of unknown origin during therapy and were separately analyzed. No patient developed advanced chronic kidney disease or clinically severe nephrotoxicity during the observation period of one year after the last therapy cycle. Excluding the two patients with urinary obstruction, no relevant deterioration in CTCAE renal grading was observed longitudinally. Although several patients demonstrated moderate decreases in eGFR over time (five patients between 10 and 30%, one patient > 30%) the overall cohort did not show a statistically significant decline in renal function.

An important aspect of the current discussion on RPT-associated nephrotoxicity concerns not only whether renal injury occurs, but also whether current diagnostic methods are sufficiently sensitive to detect early or subtle treatment-related changes. For monitoring kidney function during RPT, only few studies exist evaluating the sensitivity of eGFR and renal scintigraphy. Halkar et al. examined 21 patients without therapy comparing eGFR and ^{99m}Tc-MAG3 clearance resulting in higher precision of ^{99m}Tc-MAG3 clearance for monitoring changes in kidney function (45). Widjaja et al. examined 46 patients undergoing PSMA-RLT with superior predictive performance of pretherapeutic eGFR compared to ^{99m}Tc-MAG3 clearance (46). It should be noted that eGFR and ^{99m}Tc-MAG3 renal scintigraphy assess different components of renal function and therefore are not necessarily directly comparable, but may rather serve complementary roles in the evaluation of kidney function.

A further addition to assessment of therapy-associated renal parenchymal changes could be provided by mpMRI. To our knowledge, our study is the first to apply mpMRI for renal diagnostics during RPT. The MRI protocol was implemented according to the consensus recommendations of the PARENCHIMA consortium for standardized renal MRI (47) and has been evaluated regarding its reproducibility in a prior study with healthy volunteers (43). Although patients were significantly older than the healthy volunteers, baseline MRI examinations show comparable results supporting our assumption that patients did not have substantial renal impairment prior to initiation of therapy.

During RPT, significant longitudinal changes were found in T1, FP and CMR of BOLD. While FP and CMR of BOLD have to be interpreted with caution because of their relative high variability (43), the steady increase in T1 values may reflect expansion of the extracellular space, potentially related to mild tissue remodeling (48). T1 relaxation time has previously been identified as a sensitive biomarker for the assessment of parenchymal changes in CKD (49–51) correlating with fibrotic processes in kidneys. Notably, these alterations were not associated with measurable impairment of renal function, suggesting limited functional relevance of the observed imaging changes.

Consistent with our findings, many previous studies did not observe a clear association between absorbed renal radiation dose and subsequent renal functional decline (10, 15, 23). Historically, nephrotoxic events were observed more frequently in patients treated with ⁹⁰Y-DOTATOC compared with ¹⁷⁷Lu-based RPT (52). Furthermore, dose–toxicity correlations and commonly accepted renal radiation thresholds were largely extrapolated from EBRT experience (25).

To improve the sensitivity of detecting potential renal functional changes, patients were stratified into cohorts based on the percentage change in eGFR and analyzed separately. No significant differences in MR-derived parameters were identified between patients with stable renal function, moderate eGFR decline ≥ 10 – $<30\%$ and those with an eGFR decline $\geq 30\%$. Exploratory ROC analysis demonstrated moderate predictive performance of selected parameters for identifying patients with an eGFR decline ≥ 10 – $<30\%$. However, the predominantly preserved renal function and limited number of patients with moderate functional decline likely limited discriminatory power and may have influenced the robustness of these findings.

Interestingly, patients with urinary obstruction exhibited distinct functional imaging characteristics compared with the rest of the cohort, including lower RBF, increased BOLD and increased CMR of BOLD and T1 values. Obstructive uropathy is a well-established cause of renal hypoxia, tubulointerstitial injury, and progressive renal fibrosis (53). Experimental and clinical studies have demonstrated that chronic urinary tract obstruction induces microvascular alterations and interstitial fibrotic remodeling, which has also shown parenchymal changes in previous MR studies (54–56).

Several limitations of this study must be acknowledged. First, this was a single-center pilot study with a relatively small and heterogeneous patient cohort. Second, follow-up duration may still be insufficient to capture very late radiation-induced nephropathy. Third, longitudinal data was limited by substantial dropout rates, mainly due to oncologic disease progression and therapy discontinuation unrelated to renal function. Also, renal scintigraphy data were incomplete longitudinally and therefore could not be comprehensively integrated into all analyses. Finally, histopathological validation of the imaging findings could not be provided, as renal biopsy is a highly invasive procedure and is not part of routine diagnostic assessment during RPT.

In conclusion, except for subtle T1 alterations potentially indicating mild structural tissue remodeling, our results did not demonstrate clear evidence of clinically relevant RPT-associated deterioration in renal perfusion, diffusion, or oxygenation. Also, no significant association was observed between radiation exposure and longitudinal changes in MRI-derived structural or functional parameters. Larger prospective studies with longer follow-up are required to confirm these observations concerning the effect and safety of ^{177}Lu -based RPTs. Renal mpMRI may serve as a valuable complementary imaging tool for sensitive non-invasive renal monitoring during RPT and may improve the understanding of potential subclinical renal effects beyond conventional renal function assessment.

Declarations

Ethics approval: This prospective single-center study was approved by the local institutional review board of the medical faculty of the Eberhard Karls University of Tuebingen (126/2019B01), and all participants provided written informed consent prior to enrolment.

Consent for publication: Written informed consent to participate in the study was obtained from all participants prior to their inclusion in the study.

Consent for publication: Not applicable. The manuscript does not contain any identifiable individual participant data.

Data availability statement: The data supporting the findings of this study are available within the article. Further details and additional information are available from the corresponding author upon reasonable request.

Conflict of interests statement: The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Figures

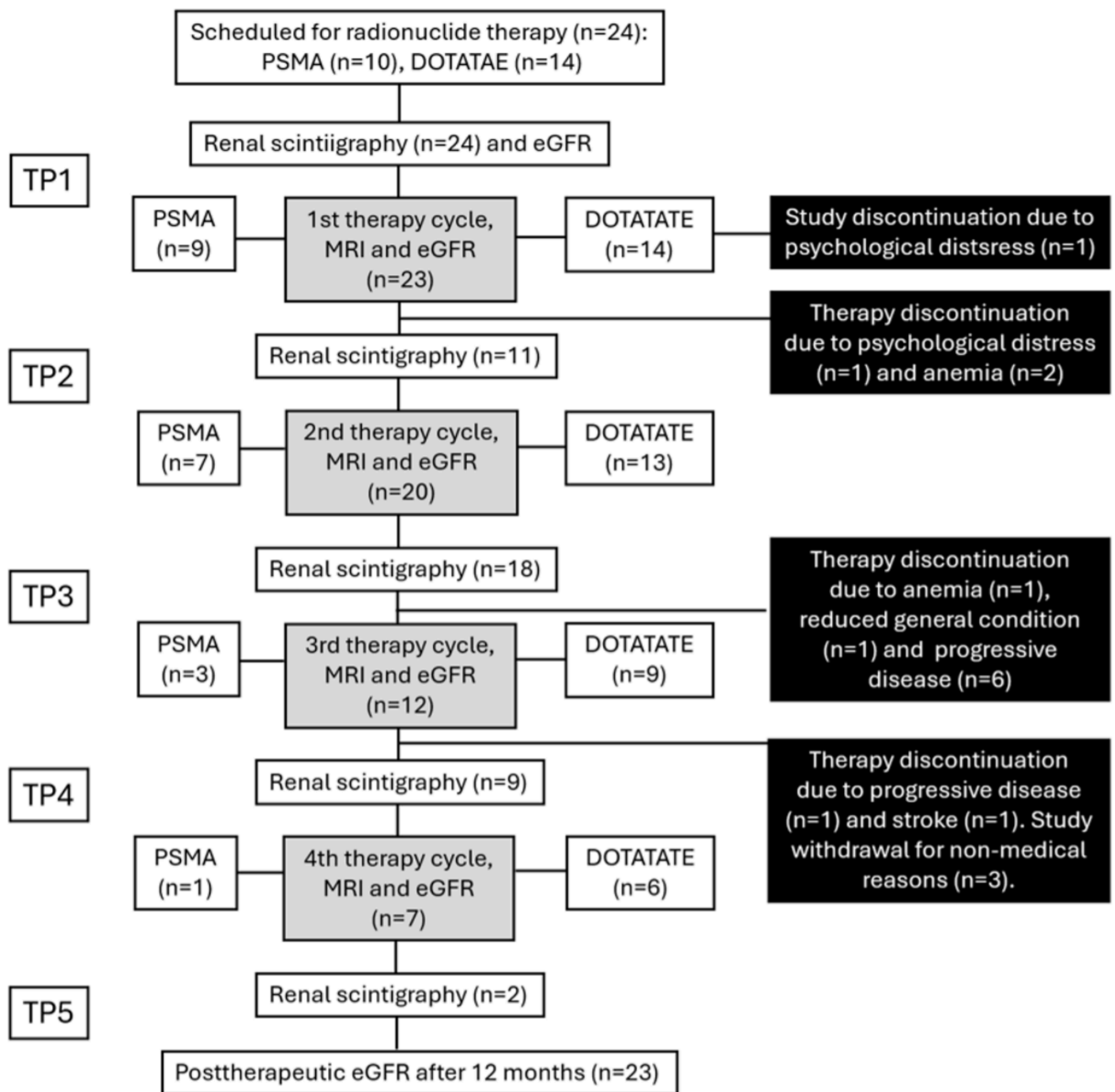


Figure 1

Clinical flowchart depicting the number of patients included at different time points (TP0-5).

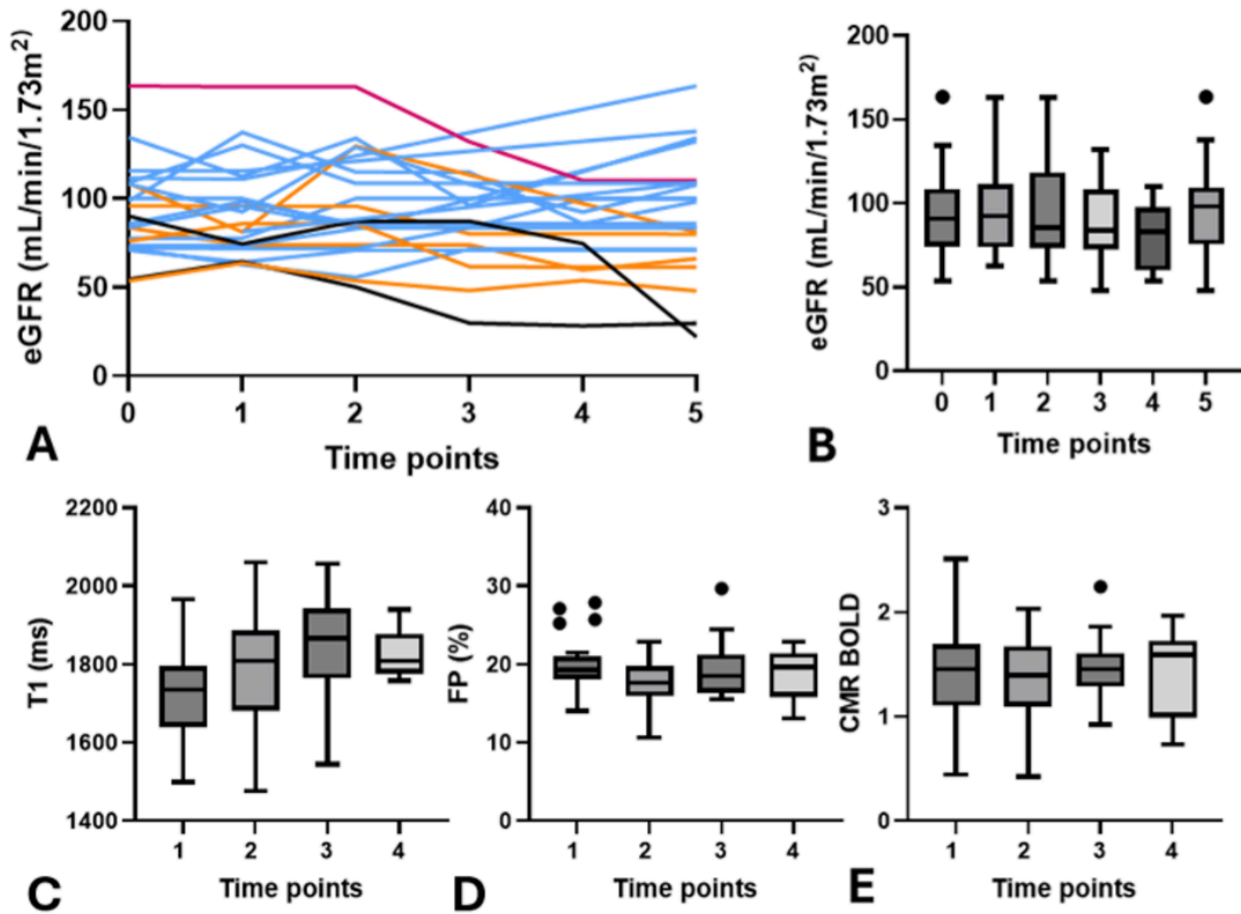


Figure 2

(A) The spaghetti plot of individual estimated glomerular filtration rate (eGFR) trajectories. 2 patients (black) developed urinary obstruction, 5 patients developed an eGFR decrease $\geq 10\%$ to $< 30\%$ (orange) and 1 patient developed an eGFR decrease $\geq 30\%$ (red) while 15 patients showed stable eGFR (blue). (B-E) Boxplots illustrate the distribution of eGFR, T1 values, perfusion fraction (FP) and corticomedullary ratio (CMR) of blood-oxygen-level-dependent MRI (BOLD) across time points. The boxes represent the interquartile range, the horizontal line indicates the median, whiskers show the range, and dots represent outliers. Patients with urinary obstruction were excluded here.

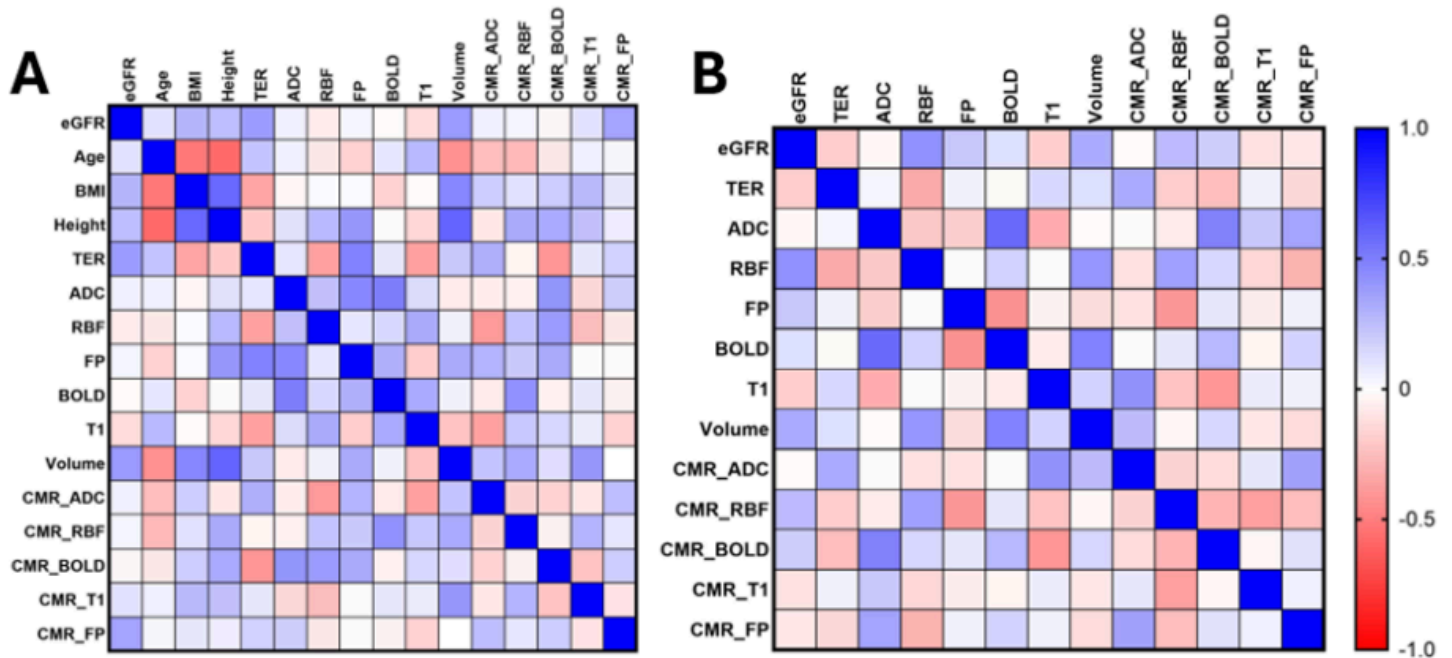


Figure 3

A: Heatmap of Spearman correlations between patient characteristics (age, BMI) and renal function parameters. B: Heatmap showing longitudinal correlations between renal function parameters. Color distribution indicates the strength and direction of correlations (Spearman ρ). Estimated glomerular filtration rate (eGFR), tubular extraction rate from ^{99m}Tc -MAG3 (TER), apparent diffusion coefficient (ADC), renal blood flow (RBF), perfusion fraction (FP), blood oxygen-level dependent (BOLD) MRI and corticomedullary ratio (CMR) of different parameters.

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Figure 4

Figure 4: Bar charts of MR of (A) renal blood flow (RBF), (B) BOLD, (C) corticomedullary ratio (CMR) of BOLD and of (D) T1 over different time points TP1-4. Error bars indicate standard deviation.

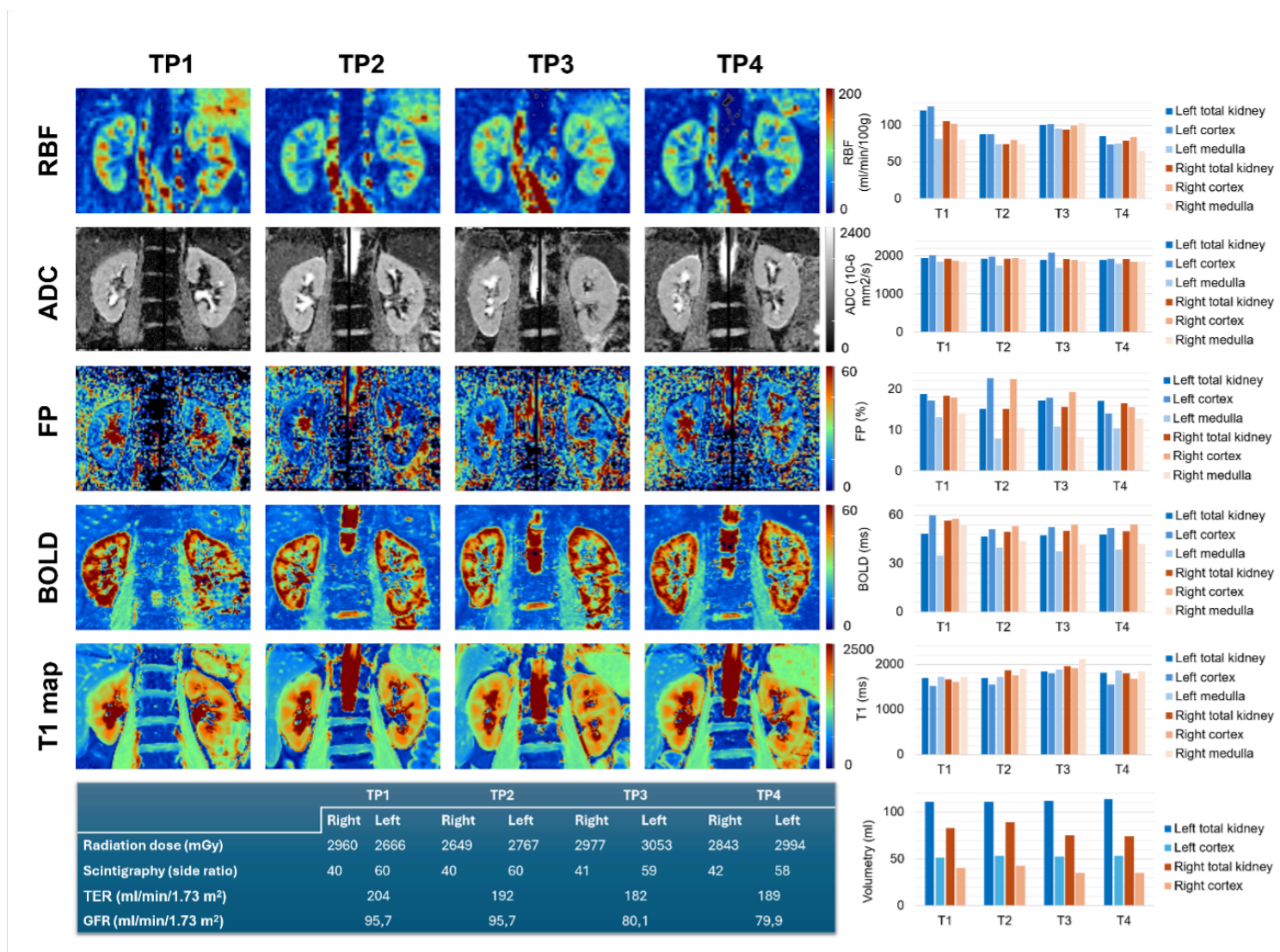


Figure 5

Figure 5: Example of a patient undergoing four cycles (TP1-4) of RPT with $[^{177}\text{Lu}]\text{Lu-DOTATATE}$. This patient developed urinary obstruction of the right kidney between the second and third therapy cycle and was treated with a double-j catheter. Interrenal differences can be observed for both tubular extraction rate (TER) and MR parameters including renal blood flow (RBF) derived from arterial spin labeling (ASL), apparent diffusion coefficient (ADC) and perfusion fraction (FP) derived from intravoxel incoherent motion (IVIM) diffusion imaging, blood-oxygenation-level-dependent (BOLD) imaging and quantitative T1. Functional parameters also demonstrate longitudinal changes particularly in eGFR, TER and RBF.

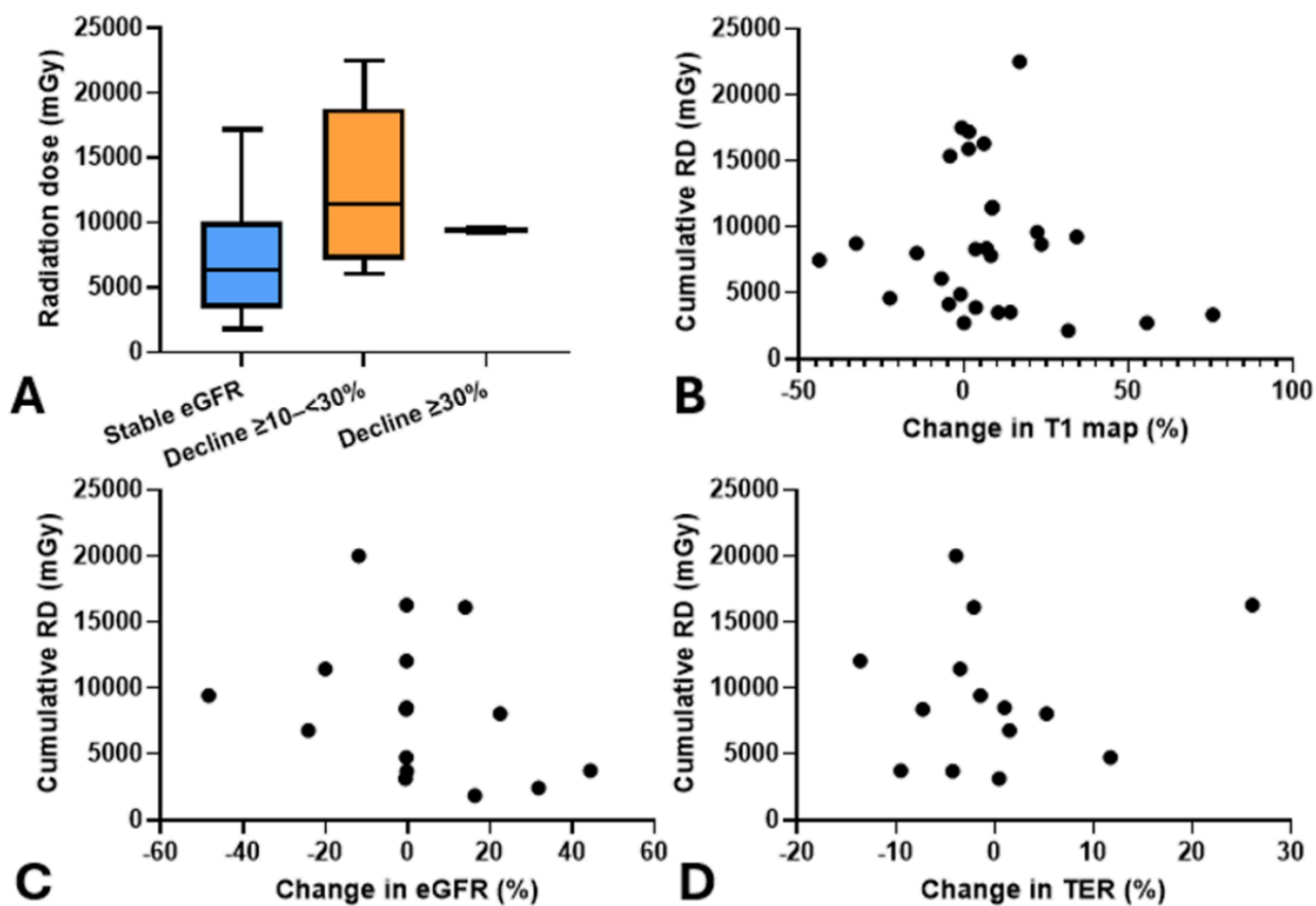


Figure 6

Figure 6: (A) Boxplots illustrating the distribution of different clinical outcomes regarding estimated glomerular filtration rate (eGFR) in relation to cumulative radiation dose in mGy. Correlation of cumulative radiation dose per kidney in mGy with kidney-specific longitudinal slope of (B) T1 values, (C) eGFR and (D) tubular extraction rate (TER) in %.

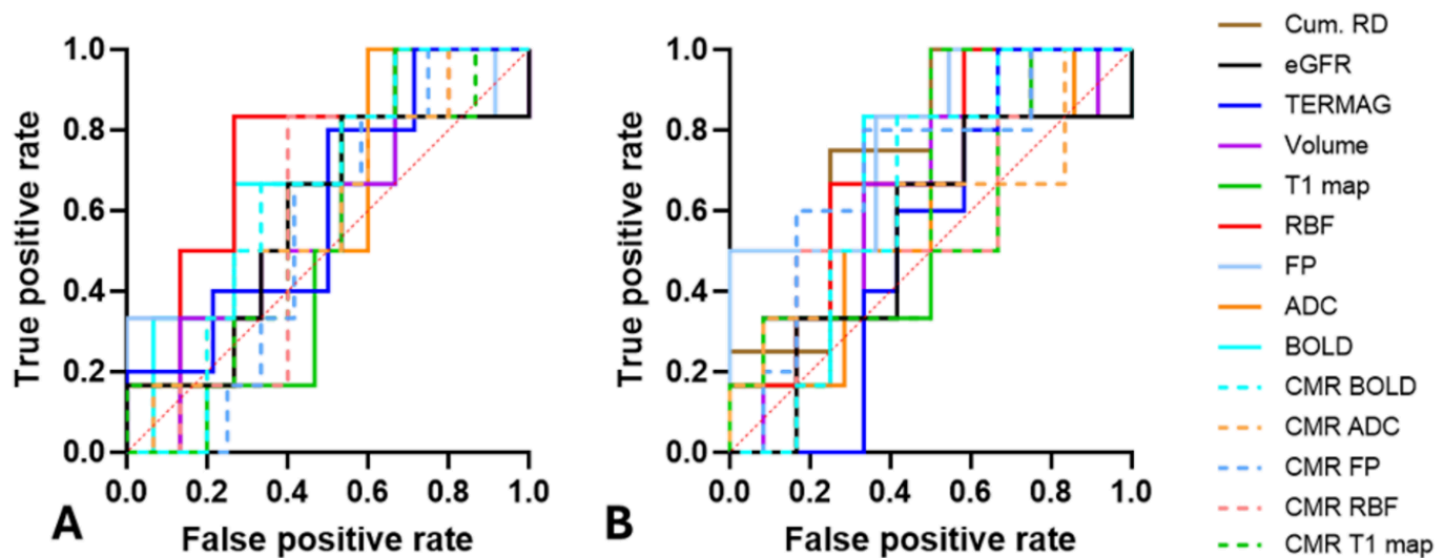


Figure 7

Figure 7: ROC curves of renal function parameters for prediction of eGFR decline ≥ 10 – $< 30\%$. A: Baseline renal function at time point 1 (TP1). B: Longitudinal parameter slope (TP1-4) and cumulative radiation dose per patient (Cum. RD).