Pretherapeutic estimated glomerular filtration rate predicts development of chronic kidney disease in patients receiving PSMA-targeted radioligand therapy

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Abstract
Background: Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) may be associated with renal toxicity. We aimed to identify predictive parameters for the development of chronic kidney disease (CKD) in patients with metastatic castration resistant prostate cancer (mCRPC) undergoing RLT.

Methods: In 46 mCRPC patients scheduled for Lu-177-PSMA-RLT, pretherapeutic estimated glomerular filtration rate (eGFR [ml/min/1.73 m²]), Tc-99m-mercaptoacetyltriglycine (Tc-99m-MAG3) clearance and baseline Ga-68-PSMA-ligand positron emission tomography (PET)-derived renal cortical uptake and PSMA-tumor volume (TV) were determined. We tested the predictive capability of these parameters and clinical risk factors for the occurrence of CKD (defined as CTCAE vers. 5.0 grade 2 or higher) during follow-up.

Results: After 4 ± 3 cycles of RLT average eGFR declined from 76 ± 17 to 72 ± 20 ml/min/1.73 m² (p = 0.003). Increased estimated renal radiation dose (eRRD) was significantly associated with renal functional decline (p = 0.008). During follow-up, 16/46 (30.4%) developed CKD grade 2 (no grade 3 or higher). In receiver operating characteristic (ROC) analysis, pretherapeutic eGFR was highly accurate in identifying the occurrence of CKD vs no CKD with an area under the curve (AUC) of 0.945 (p < 0.001; best threshold, 77 ml/min/1.73 m²), followed by Tc-99m-MAG3-derived tubular extraction rate (TER; AUC, 0.831, p < 0.001; best threshold, 200 ml/min/1.73 m²). Renal PET signal (p = 0.751) and PSMA-TV (p = 0.942), however, were not predictive. Kaplan–Meier analyses revealed adverse renal outcome for patients with lower eGFR (p = 0.001) and lower scintigraphy-derived TER (p = 0.009), with pretherapeutic eGFR emerging as the sole predictive parameter in multivariate analysis (p = 0.007).

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1 | INTRODUCTION

The prostate-specific membrane antigen (PSMA) is a type-2-transmembrane protein, which is overexpressed on prostate cancer (PC) cells and, therefore, holds great potential for PSMA-targeted imaging and therapy.1–5 Demonstrating high efficacy and safety in a first multicenter retrospective study,6 Lu-177-PSMA-radioligand therapy (RLT) has gained increasing acceptance in the therapeutic algorithm of patients afflicted with metastasized castration-resistant PC (mCRPC).7–9 The first Phase 2 study (LuPSMA) yielded consistent favorable results in a prospective setting9 and recent reports also demonstrated higher prostate-specific antigen (PSA) response rates in patients under RLT when compared to cabazitaxel considered as the next appropriate standard treatment.10 Moreover, the first results of the prospective randomized VISION study,6 Lu-177-PSMA-RLT relative to standard of care has been recently announced, demonstrating both superior radiographic progression-free and overall survival in patients treated with Lu-177-PSMA-617.11 Thus, these results will lead to a more extensive use of RLT not only in end-stage disease, but maybe also earlier in the disease course, for example, in patients with nonmetastatic CRPC.12

Increased PSMA expression, however, was also noted in kidney proximal tubules.13 Not surprisingly, initial studies in humans under RLT also reported on an increased absorbed dose to the kidneys of up 0.53–0.88 Gy/GBq,14–16 in a manner similar to somatostatin receptor-targeting radiotracers.17 Therefore, the risk for long-term renal impairment in mCRPC patients under PSMA-directed treatment has been tabulated from 4.5% to 25%.18,19 Predictors for renal functional decline post-RLT are intensively sought and previous studies identified preexisting chronic kidney disease (CKD), diabetes mellitus, or arterial hypertension, which were all associated with higher nephrotoxicity.18,19

According to current guidelines, a pretherapeutic PSMA-ligand positron emission tomography (PET)/computed tomography (CT) is mandatory before commencing RLT.9 Of note, PSMA-ligands, such as Ga-68-PSMA-11, are excreted through the kidneys,20 and the latter radiotracer may even hold potential for the determination of split-renal function.21 Moreover, when scheduling patients for Lu-177-PSMA-RLT, a pretherapeutic blood-based assessment of estimated glomerular filtration rate (eGFR) and renal scintigraphy should be performed.8 For the latter, Tc-99m-mercaptoacetyltriglycine (Tc-99m-MAG3) has been advocated to serve as a reliable estimate of the effective renal plasma flow (ERPF), yielding comparable results relative to the reference standard derived from para-aminohippuric acid infusion.22,23 In addition, Tc-99m-MAG3 provides information on split renal function, for example, to rule out obstructive nephropathies.24 Of note, recent studies also reported on a reduced renal cortical uptake in patients with higher tumor volume (TV) on both pretherapeutic 68Ga-PSMA-11 PET/CT and renal dosimetry during Lu-177-PSMA-RLT.25,26 However, the relative usefulness of these parameters for the prediction of treatment-related nephrotoxicity is poorly understood. In the present study, we aimed to evaluate the predictive performance of eGFR (obtained from blood samples), pretherapeutic Tc-99m-MAG3 clearance and PSMA-ligand PET-derived renal cortical uptake and TV for the occurrence of treatment-related CKD.

2 | MATERIAL AND METHODS

2.1 | Patient population

We included 46 patients with mCRPC in this monocentric retrospective study (Table 1). Baseline Ga-68-PSMA-11 PET/CT, pretherapeutic Tc-99m-MAG3 renal scintigraphy, and Lu-177-PSMA-RLT were performed. We recorded preexisting risk factors for the occurrence of CKD, including preexisting renal disease (prior CKD, urinary dysfunction, nephrectomy, atrophic kidney or kidney cysts; n = 18 [39%]), arterial hypertension (n = 20 [43.5%]), diabetes mellitus (n = 5 [10.9%]), and nephrotoxic drug intake (n = 37 [80.4%]), as previously described.27 This retrospective study was approved by the institutional review board (No. 9182_BO_S_2020), compliant to the Declaration of Helsinki (“unproven interventions in clinical practice”) and the German Medicinal Products Act, AMG §13.2b. We administered Lu-177-PSMA-617 after obtaining written informed consent from each patient for conducted procedures as well as for retrospective data analysis. Parts of this cohort have also been investigated in Derlin et al., and Widjaja et al.5,28,29

2.2 | Assessment of pretherapeutic Tc-99m-MAG3-derived tubular extraction rate (TER)

Before the first cycle of Lu-177-PSMA-RLT, patients underwent renal scintigraphy with Tc-99m-MAG3. Studies were performed using a
**TABLE 1** Patient characteristics (n = 46)

| Variable                                      | Value                  |
|-----------------------------------------------|------------------------|
| Age at first cycle of PSMA RLT (years, mean ± SD) | 72.2 ± 7.1             |
| Treatment cycles per patient (mean ± SD)       | 4 ± 3                  |
| Administered cumulative activity (GBq, mean ± SD) | 32.1 ± 22.6            |
| Estimated renal radiation dose (Gy, mean ± SD)  | 28.3 ± 19.9            |
| Gleason score                                  | 8 (7–9)                |
| Previous treatments (%)                        |                        |
| Radical prostatectomy                          | 67                     |
| Primary radiation therapy to the prostate      | 11                     |
| Salvage radiation therapy                      | 54                     |
| Antihormonal treatment                         | 100                    |
| Enzalutamide                                   | 61                     |
| Abiraterone acetate                            | 74                     |
| Previous chemotherapy                          | 83                     |
| Clinical risk factors (%)                      |                        |
| Preexisting renal disease<sup>a</sup>           | 39                     |
| Arterial hypertension                          | 44                     |
| Diabetes mellitus                              | 11                     |
| Nephrotoxic drugs<sup>b</sup>                  | 80                     |
| Baseline laboratory values                     |                        |
| PSA (μg/L)                                     | 231 (32.9–445.9)       |
| eGFR (ml/min/1.73 m<sup>2</sup>)               | 83 (63.3–88)           |
| Tc-99m-MAG3-derived TER (ml/min/1.73 m<sup>2</sup>) | 191 (171.3–233.5)     |
| Ga-68-PSMA-11 PET-derived SUV<sub>peak</sub>    | 19.3 (14.6–24.1)       |
| Ga-68-PSMA-11 PET-derived PSMA-TV (cm<sup>3</sup>) | 137 (31–314)          |

<sup>a</sup>Prior CKD, urinary dysfunction, nephrectomy, atrophic kidney or kidney cysts.

<sup>b</sup>Analgetics, antihypertensive medication, lipid lowering medication, furosemide intake. Gleason score, prostate-specific antigen (PSA), estimated glomerular filtration rate (eGFR), peak standardized uptake value (SUV<sub>peak</sub>), tubular extraction rate (TER), and tumor volume (TV) given as median followed by interquartile range (IQR) in parentheses; GBq, Gigabecquerel; Gy, Gray; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

2.3 | **Assessment of pretherapeutic PET-derived renal cortical uptake and PSMA-TV**

A dedicated PET/CT system (Biograph mCT 128 Flow; Siemens), equipped with an extended field-of-view PET component and a 128-slice spiral CT component, was used to acquire Ga-68-PSMA-11 PET/CTs as previously described. In patient, 105 ± 22 MBq of Ga-68-PSMA-11 were injected intravenously. 1 h after injection and after voiding of the bladder imaging started with a low-dose none-nhanced helical CT (120 kV, mA modulated, pitch of 1.2, re-constructed axial slice thickness of 5.0 mm) for attenuation correction. Whole-body PET images were subsequently acquired using continuous bed motion at a speed of 0.9 mm/s for chest and abdomen and 2.1 mm/s for legs. Reconstruction of all studies was performed using Ultra HD, an iterative algorithm combined with time-of-flight and point-spread function information (Siemens Healthcare; 2 iterations, 21 subsets; matrix, 200; zoom, 1.0; gaussian filter, 5.0). We administered no contrast material. A volume of interest (VOI) was placed in the cortex of both kidneys carefully avoiding the renal pelvis. PSMA-ligand uptake in both kidneys was then measured as peak standardized uptake value (SUV<sub>peak</sub>). In addition, we also assessed PSMA-TV (cm<sup>3</sup>) on baseline PET as described in Widjaja et al. and Schmuck et al. In 3/46 (6.5%) patients, PSMA signal of only one kidney was measurable due to nephrectomy (2/3 [66%]) or atrophic kidney (1/3 [33%]). Averaged values were used for further analysis.

2.4 | **Assessment of laboratory values and renal outcome**

Before first RLT (Cycle 1, Day 1) and during follow-up, blood collections were performed in all patients using serum-gel, lithium-heparin, and dipotassium-ethylenediaminetetraacetic acid (EDTA) Monovette<sup>®</sup> tubes (Sarstedt) and analyzed using a Cobas 800 analyzer (Roche Deutschland Holding GmbH). Creatinine was determined by photometry and PSA by sandwich immunoassays. Calculation of eGFR was performed using CKD-Epidemiology Collaboration (EPI)-formula. Analyses were conducted according to manufacturers’ instructions, as well as following our in-house procedure guidelines and standard quality assurance procedures. Last follow-up was assessed 6–8 weeks after the last included cycle of RLT. CKD was then determined according to common terminology criteria for adverse events (CTCAE) 5.0 Grade 2 (defined as eGFR between 60 and 30 ml/min/1.73 m<sup>2</sup>) or higher.

2.5 | **177Lu-PSMA RLT**

Preparation of the PSMA-targeting ligand Lu-177-PSMA-617 was performed following GMP guidelines. Until the last follow-up, patients received 4 ± 3 cycles of RLT at intervals of 6–8 weeks. A cumulative activity (CA) of 32.1 ± 22.6 GBq Lu-177-PSMA-617 was administered
intravenously. Treatment followed the European procedure guidelines for the use of PSMA-RLT.\textsuperscript{8} Patients underwent intravenous hydration with NaCl 0.9% (0.5 L before and 1 L after treatment).

### 2.6 Calculation of estimated renal radiation dose (eRRD)

Based on previously reported absorbed renal doses for 177Lu-PSMA (0.88 Gy/GBq),\textsuperscript{16} we calculated the eRRD using an equation established by Yordanova et al:\textsuperscript{19}

\[
\sum eRRD\ [Gy] = 0.88 \frac{Gy}{GBq} \times CA\ [GBq].
\]

### 2.7 Statistical analysis

Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software) and SPSS Statistics 27 Inc. (IBM). A two-sided Student’s t test was performed to compare two groups. Simple linear regression was used to determine the relation between PSMA-TV and PET-based renal SUV\textsubscript{peak}, eRRD, change of eGFR, eGFR at last follow-up, pretherapeutic eGFR, and renal scintigraphy-based TER. Cut-offs for the prediction of adverse events were determined by receiver operating characteristics (ROC) analysis using the Youden Index for optimization of sensitivity and specificity.\textsuperscript{34} We determined the relation between the occurrence of CKD and clinical parameters (including preexisting renal disease, age, diabetes mellitus, arterial hypertension, and nephrotoxic drugs), baseline eGFR (derived from blood samples), renal scintigraphy-based TER, and PET-based renal SUV\textsubscript{peak} using Fisher’s exact test. In addition, we performed univariate Kaplan–Meier analysis and nonparametric log-rank test utilizing the ROC-derived cut-offs to identify outcome differences between subgroups. Finally, multivariate logistic regression was performed to determine independent predictors of adverse events. A \( p < 0.05 \) was considered statistically significant.

### RESULTS

#### 3.1 RLT is associated with renal function decline

During follow-up of 8 ± 6 months (median: 5 months), average eGFR declined from 76 ± 17 (median: 83) at baseline to 72 ± 20 (median: 72) ml/min/1.73 m\textsuperscript{2} at last follow-up (\( p = 0.003 \)). Of note, this decline was mainly driven by patients with reduced pretherapeutic eGFR under the normal range of 90 ml/min/1.73 m\textsuperscript{2} (\( n = 36; \) baseline eGFR, 70.4 ± 14.1 to 65.3 ± 17.1 ml/min/1.73 m\textsuperscript{2} at last follow-up; \( p = 0.004 \)). In contrast, patients with normal pretherapeutic eGFR demonstrated no significant renal functional decline (\( n = 10; \) baseline eGFR, 97 ± 5.3 to 95.9 ± 8.3 ml/min/1.73 m\textsuperscript{2} at last follow-up; \( p = 0.48 \); Figure 1). Patients received 4 ± 3 cycles of RLT, leading to a CA of 32.1 ± 22.6 GBq and an eRRD of 28.3 ± 19.9 Gy at last follow-up, respectively. There was a significant correlation between higher eRRD and subsequent stronger decrease of eGFR (\( r = -0.39; \) \( p = 0.008 \)). At last available follow-up after 8 ± 6 months, 16/46 (30.4%) demonstrated CKD according to CTCAE (Grade 2, 16/16 [100%]; no Grade 3 or higher).

#### 3.2 Baseline eGFR predicts development of CKD under RLT

Lower eGFR at last follow-up was significantly associated with lower pretherapeutic eGFR (\( r = 0.89; \) \( p < 0.001 \); Figure 2A,B,D) and lower Tc-99m-MAG3-derived TER (\( r = 0.68; \) \( p < 0.001 \); Figure 2A,C,E). In ROC, pretherapeutic eGFR demonstrated the highest accuracy in identifying patients with and without CKD during RLT with an area under the curve (AUC) of 0.945 (\( p < 0.001 \); best threshold, 77 ml/min/1.73 m\textsuperscript{2}; Figure 3A). In addition, Tc-99m-MAG3-derived TER was also highly accurate in identifying the occurrence of CKD (AUC, 0.831, \( p < 0.001 \); best threshold, 200 ml/min/1.73 m\textsuperscript{2}; Figure 3B), followed by age (AUC, 0.689, \( p = 0.019 \), best threshold, 74.5 years). In contrast, the eRRD did not reach significance (AUC, 0.658, \( p = 0.053 \),
best threshold, 32.7 Gy). Investigating PSMA PET, we observed a significant inverse correlation between renal SUV peak and PSMA-TV ($r = -0.35; p = 0.017$). However, neither renal SUV peak (AUC, 0.529, $p = 0.751$, best threshold, 16) nor PSMA-TV (AUC, 0.494, $p = 0.942$, best threshold, 295 cm$^3$) reached significance in ROC-analysis for the occurrence of CKD. ROC-derived thresholds were then used for further analyses.

In univariate analysis (Table 2), pretherapeutic eGFR emerged as the strongest predictor for CKD under RLT with an odds ratio (OR) of 0.017 (95% CI: 0.002–0.152, $p < 0.001$), followed by Tc-99m-MAG3-derived TER (OR: 0.033 [95% CI: 0.004–0.29, $p < 0.001$]) and eRRD (OR: 4.22 [95% CI: 1.15–15.51, $p = 0.049$]), whereas PET-derived renal SUV peak ($p = 0.325$) and PSMA-TV ($p = 0.498$) did not reach significance. Regarding clinical risk factors, only preexisting renal disease was predictive for the occurrence of CKD (OR: 7.23 [95% CI: 1.87–28, $p = 0.004$]). In contrast, diabetes mellitus ($p = 0.325$), arterial hypertension ($p = 0.548$), age ($p = 0.126$), and nephrotoxic drug intake ($p = 1$) were not associated with development of CKD. In Kaplan–Meier analysis (Figure 3C,D), both lower pretherapeutic eGFR and Tc-99m-MAG3-derived TER were associated with shorter CKD-free survival. However, eGFR separated better between patients with and without CKD ($p=0.001$ vs. $p=0.009$ for Tc-99m-MAG3 derived TER). Finally, in multivariate logistic regression analysis (Table 2) including preexisting renal disease, eRRD, pretherapeutic eGFR and Tc-99m-MAG3-derived TER, eGFR emerged as the sole independent predictor for the occurrence of CKD with a
Figure 3 Baseline estimated glomerular filtration rate (eGFR) and Tc-99m-MAG3-derived tubular extraction rate (TER) for prediction of chronic kidney disease (CKD). Receiver operating characteristics (ROC) for the prediction of CKD for baseline eGFR (A) and Tc-99m-mercaptoacetyltriglycine (Tc-99m-MAG3)-derived TER (B). Black arrows indicate optimal cut-offs with maximum sensitivity and specificity. Kaplan-Meier curves for CKD-free survival for pretherapeutic eGFR (C) and Tc-99m-MAG3-derived TER (D) using ROC-derived cut-offs of 77 ml/min/1.73 m² for pretherapeutic eGFR and 200 ml/min/1.73 m² for Tc-99m-MAG3-derived TER. Patients with lower eGFR and TER at baseline demonstrated significantly shorter CKD-free survival. Relative to TER, blood-based eGFR separated better between patients with and without CKD.

4 | DISCUSSION

In the present study investigating Lu-177-PSMA RLT-induced occurrence of CKD in 46 patients with mCRPC, we identified pretherapeutic eGFR as the sole predictor for subsequent CKD on-set.

Lu-177-PSMA-RLT has achieved increased clinical acceptance in the therapy of patients with mCRPC demonstrating progression under standard therapy. However, due to PSMA-expression in proximal renal tubules and renal excretion, the cross-fire effect of Lutetium-177 may increase the risk of off-tumor toxicity with concomitant irradiation of healthy renal tissue. Current guidelines recommend tolerance limits of 28–40 Gy for the kidneys and recent studies reported on an absorbed dose of approximately 0.88 Gy/GBq Lu-177-PSMA. As such, up to 24.6–35.2 GBq can potentially be administered, which is equivalent to 4.1–5.9 cycles as recommended by current guidelines. Although we exceeded this limit in selected patients with exhausted therapeutic options with a mean administered CA of 32.1 ± 22.6 GBq among 4 ± 3 cycles and an eRRD of 28.3 ± 19.9 Gy, the estimated absorbed dose failed to reach significance for predicting CKD in a multivariate analysis (p = 0.148). This is in line with Yordanova et al. reporting on a cumulative renal radiation dose of 19 Gy in their study cohort, which was also not linked to an elevated incidence of nephrotoxic events under RLT. However, the established tolerance doses for the kidneys are primarily based on studies using peptide receptor radionuclide therapy for neuroendocrine tumors, and therefore, the upper limits for absorbed renal doses may substantially differ for PSMA-targeted RLT. Future studies evaluating the impact of renal absorbed doses on later kidney toxicity should also include a precise assessment of effective half-lives of the activity in the kidneys, preferably by conducting serial post-therapeutic imaging up to 6 days postinjection. As this is a relatively time-consuming approach for both patients and personnel, it could then also be assessed whether a single quantitative measurement of the abdominal
activity concentration by SPECT may already provide a reliable read-out of the absorbed doses to the kidneys.\(^{37}\)

As a major drawback, both CA and renal absorbed doses can only be taken into consideration after administration of the therapeutic compound, but predictive parameters, which are available before initiation of RLT would be highly desirable. In a recent study with an observational period of 12 months, Gallyamov et al. demonstrated that preexisting impaired renal function is associated with an increased relative risk for adverse renal outcome.\(^{18}\) This is in line with our findings in patients with preexisting renal disease. Nonetheless, preexisting disease of the kidneys was not independently associated in our rather small cohort when a multivariate logistic regression analysis was applied (HR: 1.95, \(p = 0.22\)).

### Table 2: Uni- and multivariate analysis of predictors for chronic kidney disease (CKD)

| Predictor for CKD | Univariate analysis | Multivariate analysis |
|------------------|---------------------|---------------------|
|                  | OR      | 95% CI | \(p\) value | HR      | 95% CI | \(p\) value |
| **Clinical risk factors** | | | | | | |
| Nephrototoxic drugs\(^a\) | 1.08 | 0.23–5.06 | 1 | | |
| Arterial hypertension | 1.5 | 0.44–5.09 | 0.548 | | |
| Diabetes mellitus | 3.23 | 0.48–21.74 | 0.325 | | |
| Age | 2.88 | 0.82–10.1 | 0.126 | | |
| Preexisting renal disease\(^b\) | 7.23 | 1.87–28 | 0.004\(^c\) | 1.95 | 0.22–17.67 | 0.552 |
| **Clinical parameters** | | | | | | |
| eRRD | 4.22 | 1.15–15.51 | 0.049\(^c\) | 7.05 | 0.5–99.56 | 0.148 |
| Baseline eGFR | | 0.017 | 0.002–0.152 | <0.001\(^d\) | 0.018 | 0.001–0.341 | 0.007\(^e\) |
| Tc-\(^{99m}\)MAG3 derived TER | 0.033 | 0.004–0.29 | <0.001\(^d\) | 0.08 | 0.005–1.381 | 0.082 |
| Ga-\(^{68}\)PSMA-11 PET-derived TER | 0.538 | 0.12–2.36 | 0.498 | | |
| Ga-\(^{68}\)PSMA-11 PET derived \(SUV_{peak}\) (from renal parenchyma) | 0.468 | 0.13–1.68 | 0.325 | | |

Note: For multivariate analysis, only parameters that have received significance in the univariate analysis were included.

Abbreviations: eGFR, estimated glomerular filtration rate; eRRD, estimated renal radiation dose; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; \(SUV_{peak}\), peak standardized uptake value; TER, tubular extraction rate; TV, tumor volume.

\(^a\)Analgetics, antihypertensive medication, lipid lowering medication, furosemide intake.

\(^b\)Prior CKD, urinary dysfunction, nephrectomy, atrophic kidney or kidney cysts.

\(^c\)Reached statistical significance.

...
FIGURE 4  Case example of a patient without chronic kidney disease (CKD). (A) Ga-68-prostate-specific membrane antigen (PSMA)-11 PET/CT demonstrating assessment of cortical uptake in the kidneys (MIP, maximum intensity-projection). (B) shows dorsal planar images along with (C) respective renograms of the same patient after administration of Tc-99m-mercaptoacetyltriglycine (Tc-99m-MAG3) and (D) estimated glomerular filtration rate (eGFR) at baseline (before radioligand therapy) and at last follow-up. Pretherapeutic renal scintigraphy revealed normal distribution in both kidneys on dorsal planar images during image acquisition (B) and a normal renogram for the left (dotted red line) and right kidney (green line). However, tubular extraction rate (TER) was rather low with 188 ml/min/1.73 m$^2$, which was under the receiver operating characteristics (ROC)-derived cut-off of 200 ml/min/1.73 m$^2$ for Tc-99m-MAG3-derived TER (indicative for an elevated risk of CKD). Pretherapeutic eGFR was 86 ml/min/1.73 m$^2$ (D), which was above the ROC-derived cut-off of 77 ml/min/1.73 m$^2$ (indicative for no elevated risk of chronic kidney disease [CKD]). At last follow-up, this patient did not develop CKD with a stable eGFR of 88 ml/min/1.73 m$^2$, supporting the notion that the predictive value of pretherapeutic eGFR is superior when compared to Tc-99m-MAG3-derived TER [Color figure can be viewed at wileyonlinelibrary.com]

performance of Cr-51 EDTA for RLT-associated CKD should be also tested in future studies.

Rosar et al. recently demonstrated that Ga-68-PSMA-11 PET also holds potential for the determination of split renal function.$^{21}$ Since Ga-68-PSMA-11 is mainly excreted through the kidneys, one may speculate that a quantitative assessment of renal radiotracer accumulation may also serve as a surrogate marker for the occurrence of later CKD. However, in our study, there was no association between PSMA signal on pretherapeutic PET/CT, renal function, and subsequent risk of CKD under RLT. Future studies may also investigate whether such interrelations can be detected for other PSMA-ligands, for example, F-18-PSMA-1007, or optimized imaging protocols.$^{41}$ Moreover, the relative contribution of parenchymal PSMA expression versus irradiation due to renal excretion has not been elucidated yet and should be subject of future investigations. Furthermore, future studies might also investigate whether the delta of renal cortical uptake between baseline and follow-up PSMA-PET has predictive value for subsequent development of CKD or if other PET-based parameters may be useful to identify patients prone to later renal impairment under RLT.

Previous studies demonstrated an inverse correlation between PET-derived renal cortical uptake and PET-derived PSMA-TV.$^{26}$ In line with those findings, we also detected a tumor sink effect in our study ($r = -0.35; p = 0.017$). Interestingly, Violet et al. have already reported on a reduced renal absorbed dose under Lu-177-PSMA-RLT in patients with increased TV, most likely due to a tumor sink effect under RLT.$^{42}$ Thus, one might speculate that reduced renal radiation dose due to increased PSMA-TV is linked to a lower risk for subsequent CKD under RLT. However, in the present study, PSMA-TV did not demonstrate predictive performance in univariate analysis.

Another promising therapy option for patients with mCRPC is $^{90}$Y-PSMA-RLT.$^{43}$ Because of the higher maximum $\beta$-particle energy of $^{90}$Y (2.28 MeV vs. 0.497 MeV for $^{177}$Lu) and the resulting deeper penetration depth of 3 mm (vs. 0.6 mm for Lu-177), $^{90}$Y-PSMA-RLT might improve therapy efficacy for patients with extensive tumor load.$^{43}$ Of note, Rathke et al. demonstrated a significantly higher absorbed kidney dose for patients under therapy with $^{90}$-PSMA (3.47 Gy/GBq)$^{44}$ when compared to Lu-177-PSMA (0.88 Gy/GBq).$^{45}$ Targeted alpha therapy with Ac-225-PSMA-617 is also entering the clinical arena and first studies investigating absorbed renal doses under Ac-225-PSMA-RLT report on doses of 148 Gy/GBq.$^{46}$ When compared to Lu-177-PSMA (6–8 GBq per cycle), Ac-225-PSMA is administered in rather low doses of 100 kBq per kg (leading to an administered activity of under 10 MBq per cycle in most of the patients)$^{47}$ but first studies have already demonstrated a substantial long-term renal injury in selected cases.$^{45}$ Therefore,
future studies may also investigate the predictive value of Tc-99m-MAG3-derived TER, Tc-99m-DTPA-based eGFR or eGFR from a simple blood collection in patients under Y-90-, Ac-225-, or tandem approaches with Lu-177-PsMA.

Some limitations have to be considered. Given the retrospective nature of this study, we investigated a rather small sample size with a limited follow-up. As such, our findings need to be corroborated in a larger patient population with longer follow-up, preferably in a prospective set-up. Such a study should also include full kidney dosimetry, ideally at multiple time points after administration of the therapeutic compound. However, such an approach is highly time-consuming and therefore, rather impractical in a high-volume theranostic center. RLT-related nephrotoxicity should also be evaluated using other markers of tubular function, for example, alpha-1 microglobulin derived from urine. Moreover, the majority of the investigated patients had clinical risk factors for the occurrence of CKD. However, except for preexisting renal disease, none of these risk factors reached significance in univariate analysis for the prediction of CKD. In addition, future studies should also include a more detailed analysis of renal scans, for example, by also investigating the predictive value of time-to-peak or residual activity. Recent studies have also reported on a substantial renal decline in the setting of RLT, but it cannot be ruled out that such kidney impairment may have been occurred regardless of any therapeutic intervention.

5 | CONCLUSIONS

Severe adverse renal events do not frequently occur after PSMA-targeted RLT. However, in the present study investigating the relative predictive value of blood-based eGFR, renal scintigraphy, PSMA-ligand PET, and clinical risk factors for the occurrence of moderate CKD under RLT, we identified pretherapeutic eGFR as the sole independent predictor. Of note, the latter parameter is easily to obtain by a simple blood collection directly before treatment.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors contributed to writing, critically reviewing, and approving the paper. Specific author contributions are as follows: Conceptualization: Liam Widjaja, Rudolf A. Werner, Thorsten Derlin, and Frank M. Bengel. Methodology: Liam Widjaja, Rudolf A. Werner, and Thorsten Derlin. Software: Liam Widjaja and Rudolf A. Werner. Validation: Thorsten Derlin, Tobias L. Ross, Rudolf A. Werner, and Frank M. Bengel. Formal analysis: Liam Widjaja and Rudolf A. Werner. Investigation: Liam Widjaja, Rudolf A. Werner, and Thorsten Derlin. Visualization: Liam Widjaja and Rudolf A. Werner. Supervision: Thorsten Derlin, Tobias L. Ross, and Frank M. Bengel. Project administration: Thorsten Derlin, Rudolf A. Werner, and Frank M. Bengel. Funding acquisition: Thorsten Derlin and Rudolf A. Werner.

DATA AVAILABILITY STATEMENT

The data are not publicly available because, due to the European regulations regarding data protection, we cannot make data available online or disburse them. However, all data are available for revision on-site.

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