




ORIGINAL ARTICLE

Renal outcomes of radioligand therapy: experience of ^{177}Lu -PSMA ligand therapy in metastatic castrate-resistant prostate cancer

Marat Gallyamov ¹, Danielle Meyrick¹, Jerome Barley¹ and Nat Lenzo^{1,2}¹GenesisCare Theranostics, East Fremantle, Western Australia, Australia and ²School of Medicine, University of Western Australia, Crawley, Western Australia, AustraliaCorrespondence and offprint requests to: Marat Gallyamov; E-mail: Marat.Gallyamov@genesiscare.com**ABSTRACT**

Background. Radioligand therapy (RLT) with ^{177}Lu -labelled prostate-specific membrane antigen (PSMA) ligands has been increasingly used in recent years for therapy of metastatic castrate-resistant prostate cancer (mCRPC). Studies have revealed that ^{177}Lu -PSMA ligand therapy is well tolerated and appears to cause fewer adverse effects than current standard of care third-line treatments. Notably, since ^{177}Lu -PSMA agents are predominantly excreted by kidneys, there are concerns relating to their potential nephrotoxicity and renal outcomes. Although many recent studies have focused on mostly nephrotoxic adverse reactions at up to 3-month follow-up, assessment of renal outcomes after ^{177}Lu -PSMA RLT in longer term follow-up is lacking. The aim of this study was to assess the influence of ^{177}Lu -PSMA RLT on renal function in patients treated for mCRPC at >3 months post-therapy.

Methods. In this retrospective cohort study, we assessed 195 men with progressive mCRPC who had received therapy with ^{177}Lu -PSMA as second- or third-line after standard therapeutic interventions. Patients underwent investigations with ^{68}Ga -PSMA-ligand positron emission tomography/computed tomography scan to confirm PSMA-expressing mCRPC. Eligible patients were required to have estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m², an Eastern Cooperative Oncology Group performance status score <3, no severe liver injury (as characterized by liver function tests) and no significant bone marrow dysfunction. Enrolled patients received two to five cycles of intravenous ^{177}Lu -PSMA I&T or ^{177}Lu -PSMA-617, at 6- to 10-week intervals. Renal outcomes were assessed according to Kidney Disease: Improving Global Outcomes guidelines as incidence of acute kidney injury (AKI), acute kidney disease (AKD) or chronic kidney disease (CKD). All assessments and tests were undertaken between therapy cycles and at follow-up of at least 3 months.

Results. Of 195 assessed men with mCRPC, 110 patients aged [mean \pm SD (range)] 70 \pm 8 (53–92) years were recruited into this study with median follow-up of 8 (interquartile range 5–12, minimum 3, maximum 29) months and mean baseline eGFR 81 \pm 13 mL/min/1.73 m². Pre-existing CKD was identified in 12% of patients. None of the patients experienced an AKI during RLT. Two AKD and three CKD G3a cases were identified. Analysis of possible impact of prior CKD and major risk factors (hypertension, diabetes, history of AKI) on incidence of AKD or CKD demonstrated relative risk 4.2 [95% confidence

Received: 26.4.2019; Editorial decision: 9.7.2019

© The Author(s) 2019. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

interval (CI) 1.23–14.29 and 1.91 (95% CI 1.14–3.12), respectively. However, Fisher's exact test did not reveal statistical significance of the impact of both conditions.

Conclusions. Current Lu-PSMA RLT protocols appear to carry a mild nephrotoxic risk with the rate of about 4.5%. Prior CKD is potentially the most significant risk factor of post-RLT renal dysfunction.

Keywords: acute kidney injury, chronic kidney disease, prostate cancer, PSMA, radioligand therapy

INTRODUCTION

Radioligand therapy (RLT) is a rapidly developing targeted therapeutic option for a variety of cancers. Ligands labelled with radioactive isotopes are now available for treatment of such neoplasia as lymphoma, melanoma and neuroendocrine tumours, as well as prostate cancer [1–4]. Prostate cancer is one of the most common cancers affecting the male population, having significant impact on morbidity and mortality because of its high prevalence and relatively high rate of metastatic spread, particularly in high grade tumours [5]. Castrate-resistant prostate cancer (CRPC), defined by disease progression despite castrate levels of testosterone, may present as a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease and/or the appearance of new metastases [6].

For patients who have failed initial or second-line therapies, alternative treatment is required to control disease progression. Current chemotherapy and androgen deprivation therapy (ADT) schemes are often associated with side effects. Moreover, these therapies are temporarily effective, and drug resistance often evolves [7]. These issues have stimulated the development of alternatives in terms of precision medicine such as RLT. Recent publications highlight the promise of novel theranostics agents [8–10].

Prostate-specific membrane antigen (PSMA) is overexpressed in around 90–100% of local prostate cancer lesions, along with bone, lymph node and organ metastases [11]. However, PSMA is not only specific to the prostate gland and is expressed by some non-cancerous tissues (e.g. salivary glands and proximal renal tubular cells) [12]. There is no known natural ligand for PSMA, and the reasons for its upregulation in prostate cancer remain unclear. Exogenous PSMA ligands undergo constitutive cell internalization when bound to PSMA, which therefore represents an appealing molecular target for theranostics [9].

Since 2013, an increasing number of centres worldwide have commenced employing RLT using ^{177}Lu -PSMA-617 or ^{177}Lu -PSMA-I&T [13–15]. Up to 80% of patients with metastatic CRPC (mCRPC) had a treatment response characterized by PSA decline of any degree, while reduction of PSA by 50% or more has been observed in 32–60% of patients. Numerous studies have revealed ^{177}Lu -PSMA therapy to be well tolerated, causing fewer adverse effects than other third-line treatments [15–19]. Due to the physiological expression of PSMA in kidneys and its predominantly renal excretion, there is concern about possible radiation toxicity to the kidneys that can cause both acute and long-term effects [20, 21].

However, the majority of recent publications have reported only 'instant' or very short-term renal toxicity after ^{177}Lu -PSMA-ligand treatments and there is a paucity of documented kidney function outcomes at follow-up >3 months. The aim of our retrospective observational study was to assess influence of ^{177}Lu -PSMA RLT on renal outcomes in patients treated for mCRPC with longer term follow-up.

MATERIALS AND METHODS

We designed a retrospective longitudinal cohort study, where we assessed 195 patients aged >40 years who were referred for initiation of ^{177}Lu -PSMA RLT in the period from November 2015 to May 2018. The cut-off time point for assessments was set as 31 October 2018. All patients had verified mCRPC with progressive PSMA-avid disease after standard first- or second-line treatments, including (but not limited to) radical prostatectomy, external-beam radiation therapy, ADT, second-generation anti-androgens (e.g. abiraterone and enzalutamide) or taxane-based chemotherapy (e.g. docetaxel and cabazitaxel). Patients were enrolled throughout Australia from different centres under the management of GenesisCare (previously Theranostics Australia Pty Ltd). Enrolled patients had progressive disease defined by imaging according to Response Evaluation Criteria in Solid Tumors (RECIST), or bone scan or new pain in an area of radiologically confirmed lesion, and were required to have an Eastern Cooperative Oncology Group (ECOG) performance status score <3.

All individuals underwent the following investigations before start of therapy, between cycles and at follow-up with clinically reasonable intervals: ^{68}Ga -PSMA-11 positron emission tomography/computed tomography (PET/CT) (to identify PSMA-avid disease and assess therapy efficacy), ^{18}F -fluorodeoxyglucose (FDG) PET/CT, contrast-enhanced CT of the chest, abdomen or pelvis, bone scintigraphy (where indicated) and hormone tests (thyroid and sexual). Patients with suspicious obstructive nephropathy were assessed by $^{99\text{m}}\text{Tc}$ -mercaptoacetyltriglycine (MAG3) renal scintigraphy to accurately evaluate kidney function. Within 2 weeks before and 4 weeks after each treatment, full blood count, electrolytes, renal and liver function tests, and serum PSA concentrations were measured.

All patients at the stage of referral to the initiation of the therapy had no acute or severe chronic kidney dysfunction [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²], severe liver injury [bilirubin >1.5 × upper limit of normal (ULN), or if >1.5 × ULN, normal conjugated bilirubin; aspartate aminotransferase or alanine aminotransferase <2 × ULN or <5 × ULN in the presence of liver metastases], or signs of significantly impaired bone marrow function (haemoglobin <90 g/L, platelet count <75 × 10⁹/L, neutrophil count <1 × 10⁹/L, lymphocyte count <1.5 × 10⁹/L). Recent use of potentially nephrotoxic drugs was taken into consideration but was not an exclusion criterion. Patients with follow-up <3 months or having had fewer than two treatments were excluded from the study (Figure 1).

^{177}Lu -PSMA-ligand therapy was provided to patients in strict compliance with the Australian Therapeutic Goods Administration Special Access Scheme for compassionate use. Different (but structurally similar) PSMA ligands (either '617' or 'I&T') were used at different centres (in Sydney and Perth, respectively). There has been no significant difference in biodistribution, safety or effect of these ligands in documented clinical reports [22]. The detailed description of the protocol of therapeutic procedure and other related information are presented in

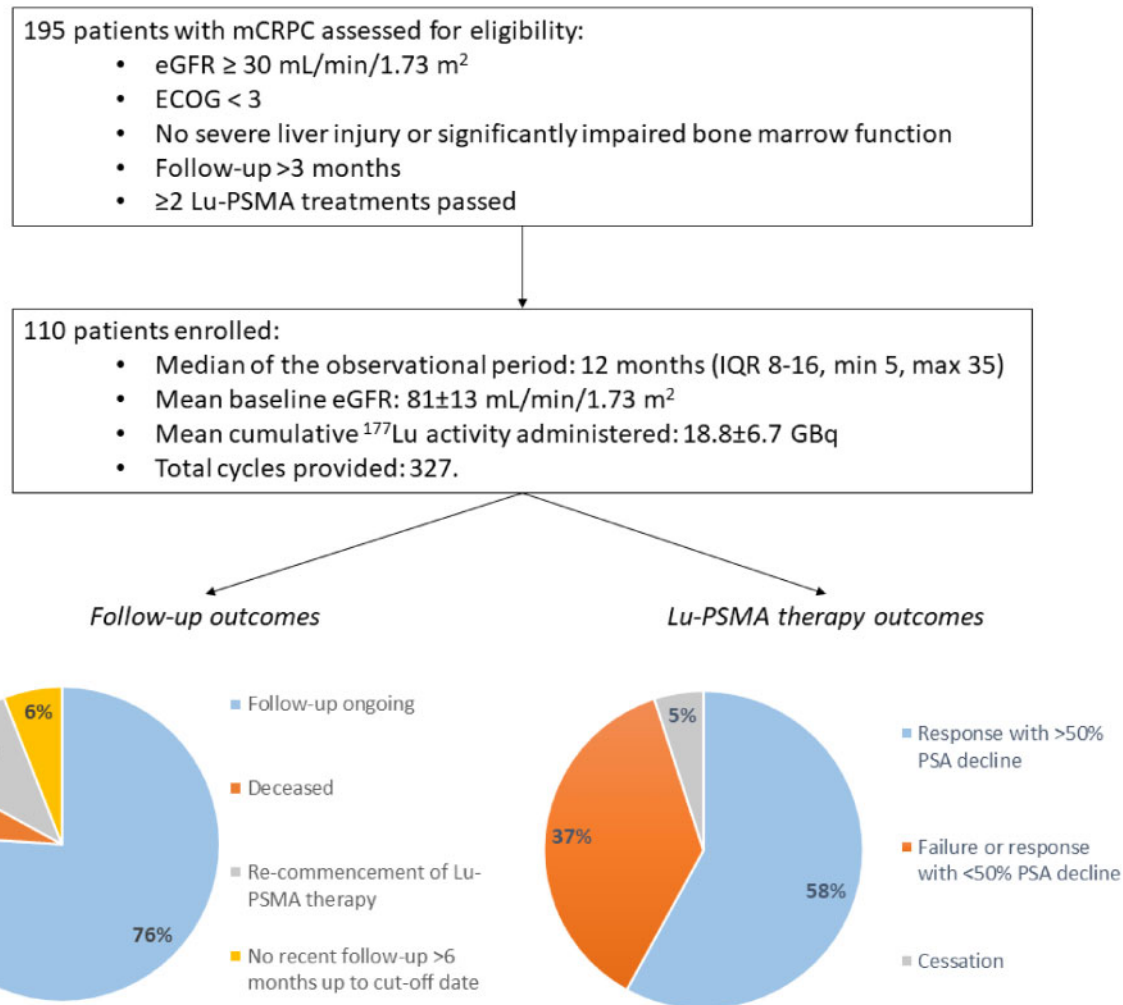


FIGURE 1: Study profile.

Supplementary data 1. The study protocol was conducted in accordance with the World Medical Association Declaration of Helsinki, the ethical standards of the institutional and national research committee and Good Clinical Practice. Before treatment entry, all individuals gave written informed consent that their data may be utilized for research purposes.

Incidence of kidney damage—acute kidney injury (AKI), acute kidney disease (AKD) or chronic kidney disease (CKD)—was assessed in compliance with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines during all observational periods. An event was considered an AKI if it occurred within 7 days of treatment, and AKD within 3 months of treatment (a decrease in GFR <60 mL/min/1.73 m² or $\geq 35\%$ with recovery of renal function close to baseline level). CKD was identified if eGFR decreased <60 mL/min/1.73 m² or GFR changed to a lower category that had been persisting for >3 months. Laboratory-reported eGFR and serum creatinine (when applicable) were the only characteristics of kidney function considered in our study [23, 24]. Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, 2017) was used as a supplementary guide to grade kidney events specifically [25]. We used the terminology of ‘major renal events’ (MRE) to mean all AKD and CKD cases.

Statistical analysis was performed using the Microsoft Office® package and freely available online statistics applications (<http://vassarstats.net/odds2x2.html>; [\[calc.org/calc\]\(https://www.quantitativeskills.com/sisa/index.htm\); <https://www.quantitativeskills.com/sisa/index.htm>\). For the assessment of correlation between two variables, we utilized the Spearman rank correlation test. Influence of risk factors on kidney damage development was evaluated by calculation of odds ratio \(OR\) and relative risk \(RR\) with 95% confidence interval \(CI\). For the assessment of a statistical significance in the analysis of contingency tables, two-tailed P-value was estimated in Fisher’s exact test. Student t-test or Mann-Whitney U test was used to compare any two groups in dependence on normality of distribution of variables. Proportions were compared by P-value calculations when applicable. Statistical significance \(compatibility\) was accepted if the P-value was \$<0.05\$.](https://www.med</p>
</div>
<div data-bbox=)

RESULTS

Patient cohort characteristics

Of 195 assessed participants with mCRPC, 110 patients aged 70 ± 8 (range 53–92) years who received two to five cycles of intravenous ¹⁷⁷Lu-PSMA RLT at 6- to 10-week intervals were recruited into this study (Figure 1). Median values with interquartile range (IQR) of the observational (starting from the first cycle) and follow-up (from the last cycle) periods were 12 (IQR 8–16, minimum 5, maximum 35) and 8 (IQR 5–12, minimum 3, maximum

29) months, respectively. Single administered ^{177}Lu activity ranged from 2.51 to 8.21 (mean 6.34 ± 1.01) GBq/patient for a total of 327 cycles provided. Mean cumulative ^{177}Lu dose was 18.8 ± 6.7 GBq. Most individuals received two or three cycles (40 and 30%, respectively); 23 and 7% of patients required four and five cycles, respectively. Fifty-nine (54%), 42 (38%) and 9 (8%) were treated by PSMA-617, PSMA-I&T and by both ligands, respectively.

Pre-existing CKD was identified in 12% (12) of patients, among which 7% had CKD G3a and 2% had CKD G3b. Hypertension (HTN), diabetes (DM), a combination of both diseases (HTN+DM) or history of AKI as major risk factors for kidney damage were present in 36% ($n=40$), 1% ($n=1$), 5% ($n=6$) and 1% ($n=1$), respectively. Mean baseline eGFR was 81 ± 13 mL/min/1.73 m² ($n=110$).

Previous ADT including standard medications or new generation androgen antagonists had been used in 85% of individuals, among which 38% had undergone chemotherapy additionally prior to the commencement of ^{177}Lu -PSMA RLT.

The remainder (15%) of study participants had received other types of the first- and second-line therapies without ADT. Regarding follow-up outcomes, the majority of patients (76%) had been continuously observed up to the cut-off date, while 6% had discontinued regular assessments for >6 months before the date. Seven per cent of individuals died due to the progression of the cancer or other concomitant diseases; there were no RLT-related deaths. Notably, some participants (11%) re-started RLT during follow-up (Figure 1).

Therapy outcomes were sorted into three categories. The first group with definitive response (>50% PSA decline from baseline according to Prostate Cancer Clinical Trial Working Group criteria) was 58% ($n=60$). The second experienced definitive failure or response with <50% PSA decline and made up 37% ($n=38$) of total. Therapy cessation due to adverse events (seizures) was observed in one patient (note that this patient did not have detectable brain metastases on ^{68}Ga -PSMA-PET/CT imaging), while concomitant but unrelated medical or non-medical issues were reasons to cease therapy in 4% ($n=4$). Treatment outcomes could not be appropriately assessed on or by the cut-off date in 6% ($n=7$) of participants (Figure 1).

Renal outcomes

None of the patients experienced AKI based on clinical review; serum creatinine level and urine output were not checked in the first 7 days after RLT cycles. Two patients developed AKD with the most significant eGFR drop of 31% (from baseline 55 to 37 mL/min/1.73 m², GFR grade from G3a to G3b) and 24% (from baseline 72 to 55 mL/min/1.73 m², GFR grade from G2 to G3a, while the last measure was even 83) within 4–6 weeks after the treatment, with full recovery closer to baseline within 1 month. One of these patients had pre-existing HTN and CKD G3a. The second had no major risk factors or prior CKD. No pharmaceutical or other interventions were required in these cases. Three patients developed CKD G3a; only one of them had signs of prior CKD G2 with HTN and DM; two had only HTN. These participants had the most significant eGFR drop of 20, 22 and 23% in comparison with baseline level. Figure 2 shows a swimmer plot displaying individual events and renal outcomes mentioned above. Two deceased patients had an episode of AKD due to progression of prostate cancer at a time point >3 months after completion of treatment. As this event was considered unrelated to RLT, it was not defined as an AKD event for the purpose of this analysis.

All patients who developed MRE underwent both ADT and taxane-based chemotherapy before commencement of ^{177}Lu -

PSMA RLT. Analysis demonstrated that groups with and without MRE appeared to be similar in rate of usage of potential nephrotoxic medication from ADT or chemotherapy, and their influence on renal outcomes is less likely ($P=0.371$). No one with MRE experienced significant prostate cancer aggravation; specifically, there were no lesions of urinary tract noticed. Essential characteristics of patients who experienced MRE versus non-experienced are presented in Table 1.

Interestingly, we found that patients who experienced kidney dysfunction had statistically significant lower baseline eGFR (65 ± 7 mL/min/1.73 m², $n=5$) than those who did not face post-therapy renal impairment (81 ± 13 mL/min/1.73 m², $n=105$) by Student's *t*-test ($P=0.007$), although the clinical importance of this finding is equivocal. There was no difference in cumulative ^{177}Lu activity and baseline PSA level between groups and no association between renal outcomes and therapy response ($P=0.646$ from Fisher's exact test), and age at referral for RLT and duration of follow-up period did not differ (Table 1). There was no significant association between cumulative ^{177}Lu activity and eGFR changes (defined as per cent difference between baseline and post-therapy mean eGFR): Spearman R-coefficient 0.189 ($P=0.27$). Furthermore, statistically significant association between renal outcomes and a type of radioligand that was utilized for treatment was not identified: a rate of MRE experienced was 6.78% (PSMA-617 only treated, $n=59$) versus 2.38% (PSMA-I&T only treated, $n=42$); $P=0.317$, mean difference 4.40% [95% confidence interval (CI) 6.36–14%].

We analysed the possible impact of prior CKD and presence of major risk factors (HTN, DM or their combination and history of AKI) on incidence of AKD and/or CKD. ORs were not significant in all calculations, while pre-existing CKD had RR 4.2 (95% CI 1.23–14.29) and major risk factors had RR 1.91 (95% CI 1.14–3.12). Additionally, RR of AKD event in the case of exposure to prior CKD and combined CKD + major risk factors was at the significant rate of 5.25 (95% CI 1.16–23.67) and 6 (95% CI 1.19–30.33), respectively. However, the estimations were not statistically significant according to Fisher's exact test (Table 2). The detailed report of these calculations with 2×2 contingency tables can be found in the Supplementary data 2.

DISCUSSION

Although there are concerns relating to potential renal toxicity caused by ^{177}Lu -labelled ligands, recent publications mostly report data of nephrotoxicity immediately subsequent to treatment cycles rather than renal outcomes in mid-to-long term follow-up [20, 21]. In our study, median follow-up was 8 (IQR 5–12, minimum 3, maximum 29) months; this is a longer period of observation than in many studies. On the other hand, at a glance, long-term renal consequences do not seem to be a significant factor in decision-making for initiation of RLT, given that patients with mCRPC typically have a poor prognosis. Nevertheless, awareness of long-term kidney effects may be important since kidney dysfunction is an evident risk factor for cardiovascular and all-cause mortality.

In our study to evaluate kidney function and kidney disease, we strictly used KDIGO consensus definitions. When reviewing previously published data, we found many inconsistencies relating to assessment of renal outcomes after RLT. Although all researchers declared that they followed CTCAE guidelines—mostly version 4.03 (2010)—it is required to clarify to what extent their approach met current KDIGO guidelines (effective from 2012), especially in defining AKI, AKD and CKD, and their incidence or progression during follow-up [23, 24]. There are no

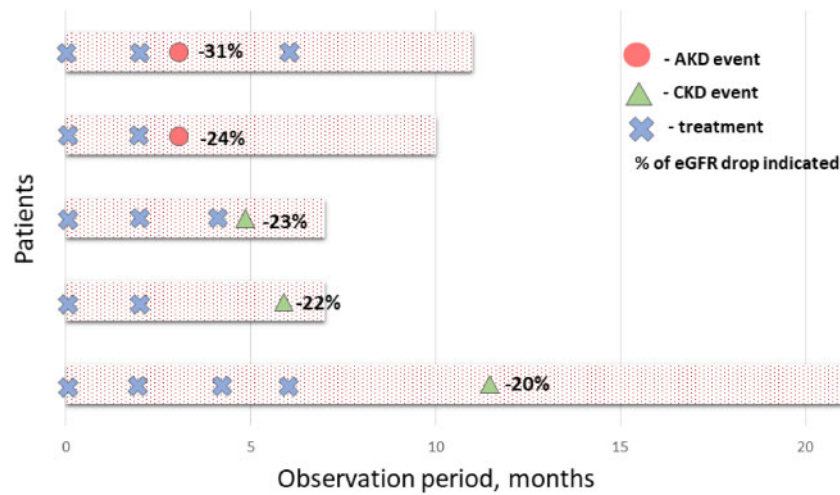


FIGURE 2: Timeline of individual events in patients with compromised kidney function after ¹⁷⁷Lu-PSMA RLT (a swimmer plot).

Table 1. Characteristics of patients that experienced versus those that did not experience an MRE

	MRE presented (n = 5)	No MRE (n = 105)	P-value
Age (years)	70 ± 6	70 ± 8	0.690
Baseline eGFR (mL/min/1.73 m ²)	65 ± 7	81 ± 13	0.007
Cumulative ¹⁷⁷ Lu activity (GBq)	19.3 ± 6.5	18.8 ± 6.8	0.459
Follow-up (months)	8 (IQR 5–9)	8 (IQR 5–12)	0.379
Baseline PSA (ng/ml)	46.4 (IQR 21–243)	86 (IQR 34–1071)	0.379
Prior hormonal or chemotherapy	100% (n = 5)	86% (n = 90)	0.371
Therapy outcomes:			
Response (>50% PSA decline)	80% (n = 4)	53% (n = 56)	0.239
Failure or response with <50% PSA decline	20% (n = 1)	35% (n = 37)	0.492

Bold values denote statistically significant.

Table 2. Influence of pre-existing CKD and major risk factors on development of AKD or CKD

Factor	Event	RR (95% CI)	P-value ^b
Prior CKD (versus no CKD)	AKD + CKD	4.20 (1.23–14.29)	0.091
Major risk factors ^a (versus no major risk factors)	AKD + CKD	1.91 (1.14–3.12)	0.193
Prior CKD (versus no CKD)	AKD only	5.25 (1.16–23.67)	0.196
Prior CKD (versus no CKD)	CKD only	3.50 (0.64–19.26)	0.278
Prior CKD + HTN (versus no CKD or HTN)	AKD only	6.00 (1.19–30.33)	0.186
Prior CKD + HTN + DM (versus HTN)	CKD only	10.00 (0.82–122.43)	0.176
HTN (versus no any risk factor)	CKD only	0.95 (0.19–4.85)	0.722

^aInclude HTN, DM, history of AKI or their combination.

^bTwo-tailed, Fisher's exact test.

Bold values denote a significant relative risk which is higher than 1.

studies to our knowledge that mentioned KDIGO or their national nephrology guidelines in this regard. Furthermore, unfortunately, in many studies, as discussed below, it is not entirely clear what type of renal impairment was detected and what approach the investigators utilized to diagnose kidney dysfunction. Some authors used terminology such as 'latent' or 'sub-acute', 'transient' or 'persistent' renal impairment, which are currently not recommended to use and are absent from both KDIGO and CTCAE guidelines. Therefore, absence of the unified diagnostic approach makes close comparison of studies difficult.

Regarding application of serum creatinine or urine output in the diagnosis of acute kidney disorders, we realize the

imperfections of their application. However, many prospective studies that investigated new biomarkers and techniques for AKI did not demonstrate significant clinical advantages in comparison with KDIGO consensus definitions [26]. A flaw of our study was the fact that serum creatinine and urine output routinely were not measured, with clinical assessment only performed in the first 7 days after each treatment. This may have led to asymptomatic AKI being overlooked. Additionally, we have not presented serum creatinine data as there were no AKI cases detected.

In our study, we revealed two cases of AKD and three cases of CKD G3a development. In terms of CTCAE, these findings are

related to Grade 1 or 2 nephrotoxicity with a rate of about 4.5%. In a review of literature, we found several single-centre studies concluding absence of renal toxicity after RLT in mCRPC patients in follow-up <3 months [17, 27, 28]. Scarpa et al. published their study of 10 patients where two patients had Grades 1–2 nephrotoxicity [29]. According to data from Heidelberg, Germany, there were no significant changes of creatinine level after a 5-month follow-up in 30 treated patients [30]. In the well-designed, phase II study of Hofman et al. [17], renal toxicity of any grade was not observed after therapy, but data were limited by the 3-month follow-up period. In a systematic review of 12 studies, including 669 patients evaluated, there were no significant renal effects revealed. However, as the authors fairly noted, their meta-analysis did not assess long-term consequences after ^{177}Lu -PSMA RLT since the included articles mostly had a short-term follow-up [18].

Experience from Bad Berka, Germany, is one of the most fascinating among other single-centre reports, and their cohort characteristics and follow-up period were relevant to our study. Researchers analysed data of 119 patients from 2013 to 2016 with follow-up of up to 34 months. There was no evidence of renal toxicity after RLT—no significant change was observed in serum creatinine, creatinine clearance (estimated by the Cockcroft–Gault formula) or tubular extraction rate as determined by $^{99\text{m}}\text{Tc}$ -MAG3 renal scintigraphy [21]. Another German group (Munster) conducted a study of 59 consecutive patients treated by ^{177}Lu -PSMA RLT with at least one cycle and follow-up from December 2014 to January 2017 (median follow-up was 24 weeks, IQR 15–36). Investigators described Grades 1–2 creatinine elevation and GFR decline in 15 (25%) and 36 (72%), respectively. There was no dysfunction greater than Grade 2 detected [31]. Unfortunately, authors from both centres did not give all details of kidney function assessment and to what extent GFR changes were related to AKD or CKD incidence. Indeed, it is required to recognize what possible causes were linked to a high rate of decline in renal function reported in comparison with other publications. Probably, these findings were due to an overestimation of the acceptable creatinine and GFR fluctuations. A similar rate of renal events was revealed by Fendler et al. during their observation up to 42 weeks [32].

A detailed investigation of renal effects of ^{177}Lu -PSMA RLT was reported by Yordanova et al. (Bonn, Germany), although it had some specific flaws and omissions [20]. The authors analysed changes in serum creatinine, serum cystatin C, glomerular filtration rate and tubular extraction rate assessed by $^{99\text{m}}\text{Tc}$ -MAG3 renal scintigraphy in 55 patients with ≥ 2 months of follow-up receiving at least 3 (IQR 3–6) consecutive cycles of ^{177}Lu -PSMA-617 every 8 weeks. Fourteen (25%) showed a sub-acute toxicity of Grade 1, while one patient had Grade 2 based on creatinine value. No Grade 3 or 4 acute loss of renal function was detected; this was in line with the German multicentre study [16]. Decreased GFR was observed in 16 patients (29%), where 4 had Grade 1 and 12 had Grade 2 toxicity. As reported additionally by researchers, significant predictors for renal function reduction were age (>65 years), arterial HTN and prior kidney disease [20]. In turn, our study showed potential influence of prior CKD or presence of major risk factors (HTN, DM and history of AKI) on incidence of MRE based on calculations of relative risk. Although our breakdown did not reveal statistical significance according to Fisher's exact test, it does not mean 'no effect' or 'no association'. Probably, some limitations of our study resulted in this inconsistency. Moreover, regarding pre-existing CKD, such an association may potentially be present since the P-value from Fisher's exact test is only 0.091 and RR

(95% CI) does not include 1, the value being much higher than 1, i.e. 4.20 (1.23–14.29). In addition, combination of pre-existing CKD and HTN may be the most significant, with a strong effect on AKD incidence separately—RR 6 (95% CI 1.19–30.33)—while HTN alone is most likely not significant to have influence on CKD development. Nevertheless, the potential link between prior CKD or other conditions and renal effects would be more accurately assessed if calculations of RR were performed in a well-designed prospective cohort study.

Our research has strengths and limitations in comparison with similar retrospective studies. The former include long-term follow-up and use of KDIGO consensus definitions for detection of renal disorders. Moreover, study design allowed us to analyse cases that were most likely not relevant to post-RLT renal toxicity to avoid an overdiagnosis of renal events. The study limitations are mostly associated with the retrospective nature of the research, although the paucity of patients with kidney disorder reduced the power of the statistical analysis as well.

To conclude, in our retrospective cohort study focused on renal outcomes potentially caused by novel ^{177}Lu -PSMA RLT, we revealed two cases of AKD, two cases of CKD G3a development and one case of CKD progression from G2 to G3a category in the cohort of 110 patients with mCRPC who had baseline eGFR >30 mL/min/1.73 m². These kidney events are considered as Grades 1–2 nephrotoxicity according to CTCAE v5.0. Hence, current ^{177}Lu -PSMA RLT protocols appear to carry a mild nephrotoxic risk with the rate of about 4.5%. It was evaluated that prior CKD was potentially more significant risk factor of post-RLT renal dysfunction than any other one investigated (HTN, DM or history of AKI), although analysis did not reveal a statistical significance in any estimations.

In the light of limitations and inconsistencies among all studies of renal effects after ^{177}Lu -PSMA RLT (including our own), prospective cohort studies with long-term follow-up are necessary to assess renal outcomes and risk factors thoroughly. Application of the nephrology guidelines should be strictly considered to allow a unified diagnostic approach and interpretation of kidney function tests, and to allow reproducibility of studies.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online

ACKNOWLEDGEMENTS

The authors thank colleagues at Diagnostic Nuclear Imaging (Perth) and Macquarie Medical Imaging (Sydney) for their role in caring for our ^{177}Lu -PSMA therapy patients. The work and support of the GenesicCare Theranostics team are gratefully acknowledged.

AUTHORS' CONTRIBUTIONS

M.G. mined data and managed database for the analysis, contributed to the study design and statistical analysis plan, searched and explored the relevant literature, and developed the first draft of the manuscript, which was critically reviewed and revised by the other authors. All other authors also contributed to the development of the study design and interpretation of data. All authors gave final approval and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

- Kraeber-Bodere F, Bodet-Milin C, Rousseau C et al. Radioimmunoconjugates for the treatment of cancer. *Semin Oncol* 2014; 41: 613–622
- Mier W, Kratochwil C, Hassel JC et al. Radiopharmaceutical therapy of patients with metastasized melanoma with the melanin-binding benzamide 131I-BA52. *J Nucl Med* 2014; 55: 9–14
- van der Zwan WA, Bodei L, Mueller-Brand J et al. GEPNETs update: radionuclide therapy in neuroendocrine tumors. *Eur J Endocrinol* 2015; 172: R1–R8
- Bodei L, Kidd M, Paganelli G et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging* 2015; 42: 5–19
- Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49: 1374–1403
- Saad F, Chi KN, Finelli A et al. The 2015 CUA-CUOG guidelines for the management of castration-resistant prostate cancer (CRPC). *Can Urol Assoc J* 2015; 9: 90–96
- Cornford P, Bellmunt J, Bolla M et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol* 2017; 71: 630–642
- Santoni M, Scarpelli M, Mazzucchelli R et al. Targeting prostate specific membrane antigen for personalized therapies in prostate cancer: morphologic and molecular backgrounds and future promises. *J Biol Regul Homeost Agents* 2014; 28: 555–563
- Haberkmorn U, Eder M, Kopka K et al. New strategies in prostate cancer: prostate-specific membrane antigen (PSMA) ligands for diagnosis and therapy. *Clin Cancer Res* 2016; 22: 9–15
- Awang ZH, Essler M, Ahmadzadehfar H. Radioligand therapy of metastatic castration-resistant prostate cancer: current approaches. *Radiat Oncol* 2018; 13: 98
- Bostwick DG, Pacelli A, Blute M et al. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer* 1998; 82: 2256–2261
- Silver DA, Pellicer I, Fair WR et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res* 1997; 3: 81–85
- Kesavan M, Turner JH, Meyrick D et al. Salvage radiopeptide therapy of advanced castrate-resistant prostate cancer with lutetium-177-prostate specific membrane antigen: efficacy and safety in routine practice. *Cancer Biother Radiopharm* 2018; 33: 274–281
- von Eyben FE, Singh A, Zhang J et al. ¹⁷⁷Lu-PSMA radioligand therapy of predominant lymph node metastatic prostate cancer. *Oncotarget* 2019; 10: 2451–2461
- Ahmadzadehfar H, Rahbar K, Kurpig S et al. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res* 2015; 5: 114
- Rahbar K, Ahmadzadehfar H, Kratochwil C et al. German multicenter study investigating ¹⁷⁷Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med* 2017; 58: 85–90
- Hofman MS, Violet J, Hicks RJ et al. [¹⁷⁷Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol* 2018; 19: 825–833
- von Eyben FE, Roviello G, Kiljunen T et al. Third-line treatment and ¹⁷⁷Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. *Eur J Nucl Med Mol Imaging* 2018; 45: 496–508
- Emmett L, Willowson K, Violet J et al. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci* 2017; 64: 52–60
- Yordanova A, Becker A, Eppard E et al. The impact of repeated cycles of radioligand therapy using [¹⁷⁷Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. *Eur J Nucl Med Mol Imaging* 2017; 44: 1473–1479
- Kulkarni HR, Singh A, Schuchardt C et al. PSMA-based radioligand therapy for metastatic castration resistant prostate cancer: the Bad Berka experience since 2013. *J Nucl Med* 2016; 57: 97S–104S
- Lütje S, Heskamp S, Cornelissen AS et al. PSMA ligands for radionuclide imaging and therapy of prostate cancer: clinical status. *Theranostics* 2015; 5: 1388–1401
- KDIGO. 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–163
- KDIGO. Clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2: 1–138
- Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) [Internet]. *Common Terminology Criteria for Adverse Events (CTCAE) v5.0*. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf (19 July 2019, date last accessed)
- Beker BM, Corleto MG, Fieiras C et al. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. *Int Urol Nephrol* 2018; 50: 705–713
- Yadav MP, Ballal S, Tripathi M et al. ¹⁷⁷Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging* 2017; 44: 81–91
- Das T, Guleria M, Parab A et al. Clinical translation of (177)Lu-labeled PSMA-617: initial experience in prostate cancer patients. *Nucl Med Biol* 2016; 43: 296–302
- Scarpa L, Buxbaum S, Kendler D et al. The ⁶⁸Ga/¹⁷⁷Lu therapeutic concept in PSMA targeting of castration-resistant prostate cancer: correlation of SUVmax values and absorbed dose estimates. *Eur J Nucl Med Mol Imaging* 2017; 44: 788–800
- Kratochwil C, Giesel FL, Stefanova M et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ¹⁷⁷Lu-labeled PSMA-617. *J Nucl Med* 2016; 57: 1170–1176
- Brauer A, Grubert LS, Roll W et al. ¹⁷⁷Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging* 2017; 44: 1663–1670
- Fendler WP, Reinhardt S, Ilhan H et al. Preliminary experience with dosimetry, response and patient reported outcome after ¹⁷⁷Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. *Oncotarget* 2017; 8: 3581–3590