Safety of Peptide Receptor Radionuclide Therapy with ^{177}Lu-DOTATATE in Neuroendocrine Tumor Patients with Chronic Kidney Disease

Shahad Alsadik[1], Gopinath Gnanasegaran[2], Luohai Chen[3,4], Dalvinder Mandair[1], Christos Toumpanakis[1], Martyn Caplin[1], and Shaunak Navalkissoor[2]

[1]Neuroendocrine Unit, Royal Free London NHS Foundation Trust, London, United Kingdom; [2]Department of Nuclear Medicine, Royal Free London NHS Foundation Trust, London, United Kingdom; [3]Department of Gastroenterology, Royal Free London NHS Foundation Trust, London, United Kingdom; and [4]First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Our purpose was to assess the efficacy and safety of ^{177}Lu-DOTATATE in neuroendocrine tumor patients with reduced renal function. **Methods:** A single-center retrospective analysis was performed on 33 patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2. Of these, 26 had chronic kidney disease (CKD) stage 3a (eGFR, 45–60 mL/min/1.73 m^2) and 7 had CKD 3b (eGFR, 30–45 mL/min/1.73 m^2). Renal toxicity and temporal changes in eGFR were recorded. The association between potential risk factors and any kidney function deterioration (>10% reduction in eGFR) was evaluated. Data on survival, the radiologic response assessment, and quality of life were collected. **Results:** The incidence of permanent grade 3 or 4 nephrotoxicity was 3% (a single patient with grade 4 nephrotoxicity). The mean annual reduction in eGFR was estimated at 2.5%. A permanent decline of less than 10% in eGFR of any grade was recorded in 45% of patients (n = 15). Nine patients moved into higher CKD categories (8 patients who moved from CKD 3a to CKD 3b and 1 patient who moved from CKD 3b to CKD 5). No significant relationship was found between renal risk factors and a permanent reduction in renal function. Grade 3 or 4 bone marrow toxicity was observed in 9% of patients. The estimated median progression-free survival was 42 mo, and the median overall survival was 47 mo. At the end of treatment, the radiologic assessment showed a partial response in 33%, stable disease in 55%, and progressive disease in 12%. There was an improvement in global quality of life and endocrine score (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Gastrointestinal NET-21) (P = 0.046 and 0.041, respectively). **Conclusion:** ^{177}Lu-DOTATATE appears to be generally well tolerated in patients with preexisting CKD 3, with a low incidence of permanent major nephrotoxicity. ^{177}Lu-DOTATATE appears to have a good therapeutic effect, with most patients reporting improvement in quality of life.

Key Words: neuroendocrine tumors; peptide receptor radionuclide therapy; PRRT; ^{177}Lu-DOTATATE; chronic kidney disease

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Peptide receptor radionuclide therapy (PRRT) has been shown to be an effective treatment modality for somatostatin receptor–expressing neuroendocrine tumors (NETs), with ^{177}Lu-DOTATATE PRRT receiving marketing authorization by the U.S. and European Union regulators in 2018 and 2017, respectively, following the successful outcome of the NETTER-1 trial (*1*). The NETTER-1 study and other large-cohort studies have shown that ^{177}Lu-DOTATATE is an effective treatment in patients with somatostatin receptor–expressing NETs, with progression-free survival (PFS) of between 2 and 3 y (*1–4*). ^{177}Lu-DOTATATE is generally well tolerated, with a low incidence of significant grade 3 or 4 toxicities. The bone marrow and the kidneys have been considered the critical organs for PRRT (*5*).

The main mechanism of absorption of the PRRT radiation dose by the kidney is partial reabsorption of the radiopeptide in the proximal tubules after glomerular filtration and retention in the renal interstitium. This process is mediated by cubilin-dependent megalin receptor endocytosis at the proximal tubules (*6*). Renal radiopeptide retention can lead to excessive renal irradiation to the radiosensitive glomeruli, with potential subsequent deterioration in kidney function. Expression of somatostatin receptor on the proximal tubules is a minor mechanism that contributes to the total renal radiation dose (*7*).

In the early years of ^{90}Y-based PRRT, significant renal toxicity (grade 3 or 4) was recorded in up to 14% of patients who received a cumulative administered activity of more than 7,400 MBq/m^2 (*8,9*). The incidence of renal toxicity has significantly decreased with the coinfusion of positively charged amino acids such as L-lysine or L-arginine, which competitively inhibit the reabsorption of the radiopeptide. This amino acid coinfusion has reduced the renal radiation dose by up to 65% (*8,9*). There is lower renal toxicity with the shorter-ranged β-particles of ^{177}Lu than ^{90}Y, leading to reduced irradiation of the radiosensitive glomeruli. Despite amino acid–based renoprotection, ^{177}Lu-PRRT still results in an approximately 3.8% annual loss of kidney function, which is lower than the 7.3% yearly decline with ^{90}Y-PRRT described by the same group (*10*).

The ^{177}Lu-DOTATATE summary of product information had previously recommended ^{177}Lu-DOTATATE in patients with an estimated glomerular filtration rate (eGFR) of more than 50 mL/min/1.73 m^2 (*11*). The latest update of the summary of product information, in 2021, recommended a change in the cutoff of baseline creatinine clearance from at least 50 mL/min/1.73 m^2 to at least 40 mL/min/1.73 m^2, presumably based on feedback from treating clinicians (*5*).

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For correspondence or reprints, contact Shaunak Navalkissoor (s.navalkissoor@nhs.net) or Shahad Alsadik (s.alsadik@nhs.net).
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There is no large dataset on PRRT toxicity in patients with stage 3 chronic kidney disease (CKD). Most of the currently published studies explore the renal toxicity of PRRT in patients with normal or mildly reduced renal function. It has been shown that patients with lower renal function have a higher renal absorbed dose per administered activity and thus are potentially at higher risk for renal toxicity (*12*). In this study, we set out to evaluate the incidence and clinical significance of hematologic and permanent renal toxicity after ^{177}Lu-DOTATATE in patients with reduced renal function (i.e., patients with an eGFR of 30–60 mL/min/1.73 m^2).

MATERIALS AND METHODS

All procedures involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Declaration of Helsinki. The institutional review board approved this retrospective study, and the requirement to obtain informed consent was waived.

We evaluated the baseline eGFR in all patients (n = 395) treated with ^{177}Lu-DOTATATE from May 2012 to August 2019 at the Royal Free London NHS Foundation Trust. Patients with CKD3 based on eGFR had a confirmatory ^{99m}Tc-diethylenetriaminepentaacetate glomerular filtration rate (GFR) determined at baseline as per routine clinical practice. We collected clinicopathologic, survival and health-related quality-of-life (HRQoL) data.

PRRT Protocol

The inclusion criteria included histologically confirmed, unresectable metastatic NETs with progressive disease. In addition, the pretherapy ^{68}Ga-DOTATATE study had to demonstrate sufficient tracer uptake (Kenning score, 2 or more). Patients had to have adequate bone marrow function and a GFR of more than 30 mL/min/1.73 m^2.

^{177}Lu-DOTATATE was administered at a target activity of 7.4 GBq per cycle to complete 4 cycles at an interval of 8–12 wk between cycles. Renal protection was implemented with standard amino acids (2.5% lysine and 2.5% arginine in 1 L of 0.9% NaCl; infusion rate, 250 mL/h) along with pretherapy antinausea medication (ondansetron, 30 mg).

Serum creatinine, eGFR, and full blood counts were calculated at baseline (on the day of the first cycle of PRRT), at 2- to 4-wk intervals between cycles, up to 8 wk after the last cycle, and at 3-month intervals thereafter.

CKD Classification

CKD was classified as CKD 1 (eGFR $\leq$ 90 mL/min/1.73 m^2, but with urine findings, structural abnormalities, or genetic traits pointing to kidney disease; for the purpose of this study, eGFR $\geq$ 90 counted as normal), CKD 2 (eGFR $\geq$ 60 to $<$ 90 mL/min/1.73 m^2), CKD 3a (eGFR $\geq$ 45 to $<$ 60 mL/min/1.73 m^2), CKD 3b (eGFR $\geq$ 30 to $<$ 45 mL/min/1.73 m^2), CKD 4 (eGFR $\geq$ 15 to $<$ 30 mL/min/1.73 m^2), or CKD 5 (eGFR $<$ 15 mL/min/1.73 m^2 or on dialysis) (*13*). Potential risk factors for renal toxicity, including age greater than 65 y, number of cycles, hypertension, diabetes, and previous chemotherapy or ^{90}Y, were identified and assessed.

HRQoL

Patients undergoing ^{177}Lu-DOTATATE treatment had HRQoL data prospectively collected as part of routine clinical practice. HRQoL was evaluated using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Gastrointestinal NET-21 (*14*). HRQoL was assessed before ^{177}Lu-DOTATATE and after each cycle of ^{177}Lu-DOTATATE. The scores were transformed to 0–100 scales, and the mean scores after each treatment were compared with the baseline scores.

Statistical Analysis

Median PFS and median overall survival with corresponding 95% CIs were estimated using the Kaplan–Meier method with the statistical software package SPSS (version 27.0; IBM). PFS was defined as the time from treatment initiation to tumor progression or death.

An objective tumor assessment on CT or MRI was performed at baseline, after cycle 2, and 3 mo after the final cycle. Afterward, CT or MRI was performed every 6 mo. We performed a radiologic response assessment after the last treatment cycle. Imaging consisted of CT or MRI and was compared with baseline imaging using RECIST, version 1.1 (*15*).

TABLE 1
Clinicopathologic Patient Characteristics

Characteristic	*n*
Sex	
Female	17 (52%)
Male	16 (48%)
Age group	
<65 y	17 (52%)
≥65 y	16 (48%)
Primary site of origin	
Gastrointestinal	21 (64%)
Pancreatic	6 (18%)
Other sites	2 (6%)
Unknown	4 (12%)
Grade	
1	14 (43%)
2	16 (48%)
3	1 (3%)
Unknown	2 (6%)
Pre-PRRT treatment	
Somatostatin receptor analogs	32 (97%)
Surgery	15 (45%)
Chemotherapy	8 (24%)
Locoregional	2 (6%)
Radiotherapy/^{90}Y-PRRT	4 (12%)
Sunitinib or everolimus	3 (9%)
Sites of metastasis	
Liver	31 (94%)
Bone	18 (55%)
Lymph nodes	24 (72%)
Peritoneum	8 (24%)
Risk factors for renal toxicity	
Hypertension	18 (22%)
Diabetes	9 (17.6%)
Chemotherapy	8 (24%)
^{90}Y-PRRT	3 (6%)
Number of ^{177}Lu cycles	
<4	7 (21%)
4	26 (79%)

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events scoring system, version 5.0 (*16*). We also assessed the effect of PRRT on renal function by calculating the annual reduction in eGFR and by the change in CKD categories.

The Fisher exact test was used to test the relationship between potential risk factors (age > 65 y, hypertension, diabetes, pre-PRRT chemotherapy, age, and previous ^{90}Y-PRRT) and renal function deterioration (reduction in eGFR of >10%). *P* values of less than 0.05 were regarded as statistically significant.

Paired Wilcoxon signed-rank testing was used to compare the HRQoL before and during ^{177}Lu-DOTATATE treatment. The scores were transformed to 0–100 scales, and the average scores after each treatment were compared with baseline scores.

RESULTS

We identified 33 patients (8%) with CKD 3 (eGFR < 60 mL/min/1.73 m^2). Of these 33 patients, 26 patients had CKD 3a and 7 patients had CKD 3b. We followed these 33 patients for a median of 38 mo (range, 13–73 mo),

The clinicopathologic features are summarized in Table 1: 17 patients were female and 16 were male, with mean age of 65 y (range, 45–81 y).

The average administered activity of ^{177}Lu-DOTATATE was 7.2 GBq per cycle. Most patients (n = 26) completed 4 cycles of treatment, with 3 patients having 3 cycles and 4 patients having 2 cycles (Table 1). The reasons for stopping treatment early in the 7 patients who had fewer than 4 treatment cycles were radiologic progression in 4, clinical deterioration in 2, and prolonged bone marrow toxicity in 1.

Common Terminology Criteria for Adverse Events grade 3 or 4 renal toxicity was recorded in 3 (9%) patients, all of whom completed 4 treatment cycles. Two of these patients developed acute kidney injury due to acute terminal events (1 patient developed sepsis; the other developed acute clinical deterioration and dehydration). The eGFR of these 2 patients was stable before these acute events. One patient (3%) developed a gradual decline in kidney function and eventually began hemodialysis.

Permanent renal function deterioration (i.e., a reduction in eGFR of >10%) was seen in 15 patients (45%) by the end of the follow-up (Table 2). Kidney function improvement (eGFR increase by >10%) was seen in 2 (6%) patients. The remaining 16 (48%) patients had no significant change in their eGFR (Fig. 1).

The average annual eGFR reduction was 2.5% per year. Overall, 9 patients moved to a higher CKD category, with 8 patients moving from CKD 3a to CKD 3b and 1 patient from CKD 3b to CKD 5. There was no significant difference in toxicity profile between patients with baseline CKD 3a and CKD 3b.

We evaluated the role of known potential risk factors for renal toxicity (age > 65 y, hypertension, diabetes, previous chemotherapy, and previous ^{90}Y-PRRT) and found no statistically significant factor (P = 0.56, 0.56, 0.57, 0.24, and 0.20, respectively). The presence of multiple renal risk factors was also not a statistically significant predictor of renal toxicity (P = 0.27).

Bone marrow toxicity (excluding lymphopenia) of any grade was recorded in 16 patients (48%). Grade 3 or 4 bone marrow toxicity (excluding lymphopenia) was recorded in 3 patients (9%); grade 3 anemia, in 2 (6%); grade 3 leukopenia, in 1 (3%); grade 3 thrombocytopenia, in 1 (3%); and grade 3 or 4 lymphopenia, in 4 (12%) (Table 3).

TABLE 2
Risk Factors for Patients with Significant (>10%) Absolute Change in eGFR After Treatment with ^{177}Lu-DOTATATE

Patient no.	Age (y)	Treatment cycles (*n*)	Cumulative administered dose (MBq)	Risk factors for renal toxicity	Baseline eGFR (mL/min/1.73 m^2)	Last recorded eGFR (mL/min/1.73 m^2)	Follow-up (y)	Annual % eGFR loss
1	64	4	30,689	HTN, DM	43	36	2.16	7.55
2	49	4	30,291	—	49	39	2.68	5.48
3	70	4	30,000	Age > 65, HTN	48	41	1.66	8.78
4	46	2	15,200	Chemotherapy, ^{90}Y-PRRT	56	49	1.01	12.36
5	57	2	14,878	Age > 65,^{90}Y-PRRT	43	34	5.12	4.09
6	81	4	29,708	Age > 65, HTN	39	15*	2.93	21.01
7	76	4	29,708	Age > 65, HTN	53	37	2.78	10.88
8	62	4	29,309	—	48	35	3.08	8.80
9	69	4	29,901	Age > 65, HTN, DM	49	44	4.66	2.19
10	73	4	28,791	Age > 65, chemotherapy	53	38	3.26	8.69
11	59	4	28,424	HTM, DM, chemotherapy	58	51	3.20	3.77
12	79	4	29,761	Age > 65	56	39	3.64	8.33
13	57	4	29,793	Chemotherapy	48	33	3.99	7.84
14	68	4	30,970	Age > 65, HTN, chemotherapy	51	44	2.28	6.02
15	67	4	29,690	Age > 65	58	52	3.38	3.06

*Required hemodialysis.
HTN = hypertension; DM = diabetes mellitus.

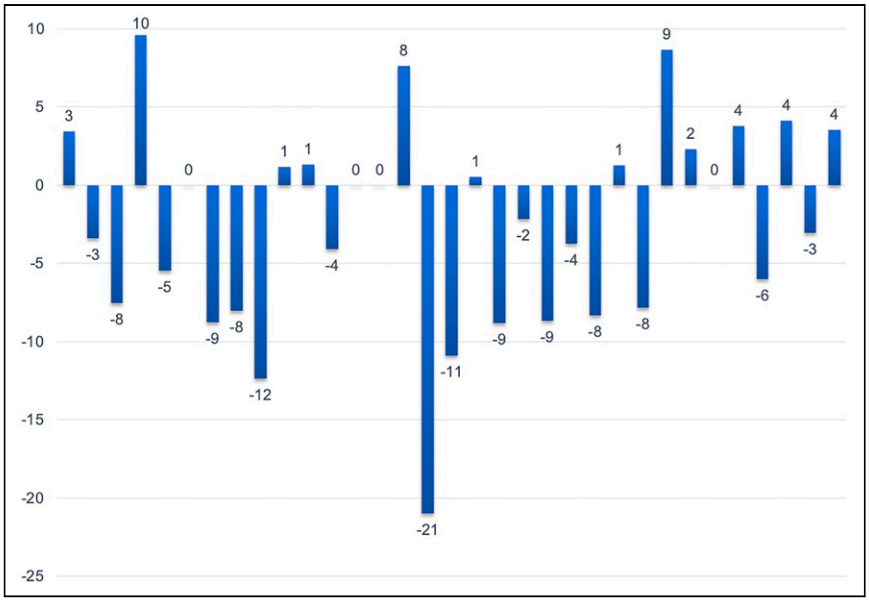

FIGURE 1. Clustered column graph representing annual percentage change in eGFR after ^{177}Lu-DOTATATE treatment.

Survival analysis showed that the estimated median PFS for the entire cohort (n = 33) was 42 mo (95% CI, 36–47 mo) and the estimated median overall survival was 47 mo (95% CI, 37–57 mo). The number of patients who died by the end of follow-up was 16 (49%). The median follow-up time was 38 mo (range, 13–73 mo).

End-of-treatment RECIST radiologic response assessment showed a partial response in 33% (n = 11), stable disease in 55% (n = 18), and progressive disease in 12% (n = 4).

HRQoL analysis in our cohort showed a significantly improved quality of life after ^{177}Lu-DOTATATE based on the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Gastrointestinal NET-21.

The overall average score improved from a baseline of 29.36 to an average of 24.93 (P = 0.046) based on paired Wilcoxon signed-rank testing. The other main area of improvement was the endocrine score, which improved from 22.64 to 17.16 (P = 0.041). The gastrointestinal symptom score decreased from 22.82 to 20.79 (P = 0.440). The average disease-related worries score decreased from 50.42 to 44.55 (P = 0.082). The average social functioning score decreased from 41.88 to 38.28 (P = 0.337) (Fig. 2).

DISCUSSION

PRRT with ^{177}Lu-DOTATATE is an established therapeutic option for advanced, metastatic well-differentiated NETs. It has gained increasing popularity because of its efficacy and relatively favorable safety profile. However, safety data for PRRT in patients with reduced renal function are limited. Caution has been advised in treating patients with reduced renal function because of the possibility that permanent renal dysfunction will develop (*11*).

The main aim of this study was to assess the safety and efficacy of ^{177}Lu-DOTATATE in patients with baseline CKD 3. No acute radiation nephritis was noted in our cohort. Of the 3 patients with grade 3 or 4 nephrotoxicity after PRRT according to the Common Terminology Criteria for Adverse Events, 1 (3%) can potentially be attributed to PRRT. Kidney function gradually deteriorated in this patient, and CKD 5 eventually developed, requiring dialysis over 3 y. The decline in kidney function was attributed to persistent vomiting with poor oral intake, but we could not exclude a contributory role of PRRT. Our finding of 3% incidence of grade 3 or 4 nephrotoxicity is slightly higher than the 0%–1.5% found in other studies (*1–3,17–20*).

Less than half our patients (n = 15) developed a reduction in kidney function by the end of the study (>10% drop in eGFR). We did not find any statistically significant correlation between clinical risk factors and reduced renal function. Similarly, other studies have not found any consistent risk factors to identify an increased risk of reduced renal function in patients undergoing treatment with ^{177}Lu-DOTATATE (*21,22*). It would, however, be prudent to be cautious in treating patients with reduced renal function and multiple renal risk factors.

We found that 2 patients (6%) had an improvement in their kidney function. One of these patients had a mesenteric mass compressing a horseshoe kidney. The subsequent reduction in the size of the mesenteric mass reduced the renal compression and resulted in better renal perfusion, which is likely the cause of the improvement in function. The second patient's improvement in eGFR was likely related to improvement in general clinical condition after a PRRT-related tumor response. The patient's overall HRQoL score improved from 28.3 to 15.0.

TABLE 3
PRRT-Related Hematologic Toxicity in Patients with CKD 3

Grade	Anemia	Leukopenia	Thrombocytopenia	Lymphocytopenia
1	10 (30%)*	1 (3%)	7 (21%)	4 (12%)
2	4 (12%)	4 (12%)	2 (6%)	8 (24%)
3	2 (6%)	1 (3%)	1 (3%)	4 (12%)
4	0 (0%)	0 (%)	0 (0%)	0 (0%)

*Six patients with baseline hemoglobin < lower normal limit.

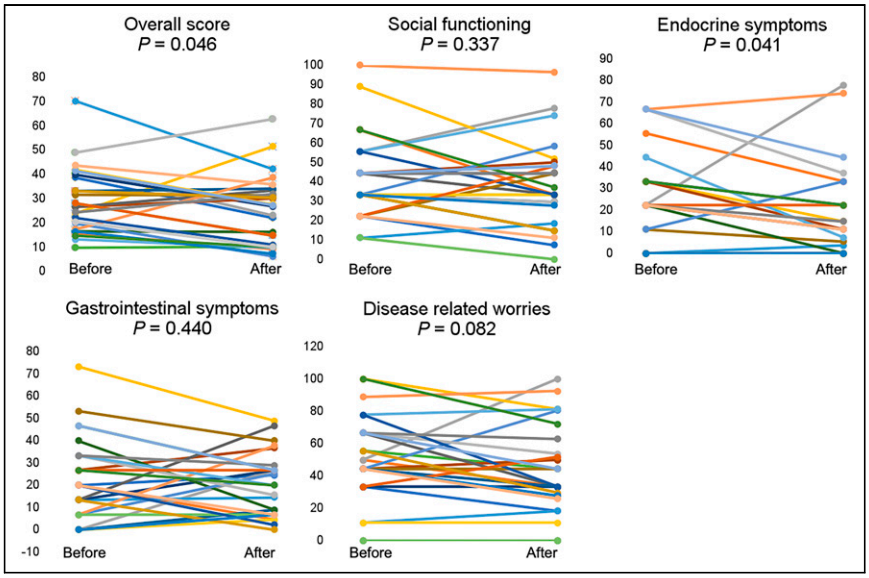

FIGURE 2. Comparison of HRQoL before and after ^{177}Lu-DOTATATE treatment.

The average annual eGFR drop was 2.5%. This result is in line with other ^{177}Lu-PRRT studies on patients with normal or mildly reduced eGFR. These studies reported an annual eGFR loss of less than 4% (*10,22*). Extrapolating these results, if we consider a hypothetical patient who had an average 2.5% eGFR loss per year and started at a baseline eGFR of 30 mL/min/1.73 m^2, this patient would need more than 10 y after ^{177}Lu-DOTATATE to reach CKD 5 and potentially require dialysis. However, if the patient were at the higher end (10%) of annual eGFR loss (which occurred in 3 patients; i.e., <10% of our cohort), the time to reach CKD 5 would decrease to approximately 6–7 y. In the worst-case scenario, if the patient lost more than 20% of baseline eGFR per year (which occurred in a single treated patient), the patient would reach CKD 5 in approximately 3 y (Fig. 3).

Longitudinal studies have shown that GFR declines steadily with age, beginning at age 30–40 y and further declining after age 65–70 y (*23*). The average GFR decline calculated in one study was estimated at approximately 0.75 mL/min/y. Some of the reduction in GFR may be due to the physiologic process of cellular senescence, which is more marked in older patients (*24*). However, in patients with more than a 10% reduction in GFR, physiologic decline alone would not explain the drop.

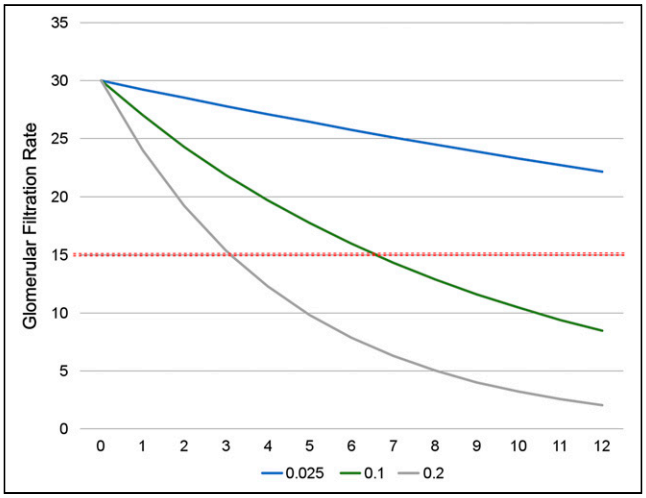

FIGURE 3. Hypothetical drop in GFR from baseline of 30 mL/min/1.73 m^2 at different percentages (2.5%, 10%, and 20%) over time after ^{177}Lu-DOTATATE treatment.

Grade 3 or 4 bone marrow toxicity in our cohort was 9%. This is slightly higher than in our overall cohort (7%) or in the NETTER-1 study (2%). This difference could probably represent a higher bone marrow dose due to prolonged radiation exposure from longer circulating radiopeptides in patients with reduced renal excretion. Similarly higher amounts of grade 3 or 4 bone marrow toxicity have been reported in other studies on patients with impaired renal function (*25,26*).

Survival analysis of our 33 patients showed that the estimated median PFS and median overall survival were 42 mo (95% CI, 36–47 mo) and 47 mo (95% CI, 37–57 mo), respectively. The PFS was greater than for the overall cohort of 395 patients at our center (PFS, 33 mo; 95% CI, 28–36 mo). The prolonged circulation time of radiopeptides may have resulted in a higher absorbed tumor dose, which potentially resulted in longer PFS. However, tumor dosimetry was not performed in this study.

The disease control rate was 88%, which is acceptable in patients with progressive advanced metastatic NETs, some of whom will have few other treatment options because of reduced renal function.

PRRT has been shown to improve the quality of life of patients with NETs (*1,27,28*). Similarly, our study showed a quality-of-life improvement in patients with CKD 3 after ^{177}Lu-DOTATATE treatment. ^{177}Lu-DOTATATE was shown to significantly improve the overall quality-of-life score ($P = 0.046$) and the endocrine symptom score ($P = 0.041$). These data further support the use of ^{177}Lu-DOTATATE in patients with reduced renal function.

There were a few limitations to this study; first, it was retrospective and thus had the associated inherent biases (e.g., selection bias and lack of follow-up). However, we felt it would be useful to report real-world data. Second, the sample size was relatively small. However, PRRT with ^{177}Lu-DOTATATE in patients with reduced renal function is considered a relative contraindication, and we feel these data may be valuable to other centers. Given that this was a retrospective study and of relatively small sample size, confirmation of these findings in a larger prospective, multicenter study with a formal sample-size calculation would be useful. Third, because of problems in obtaining funding, some patients were treated after a delay or as a later treatment line, potentially reducing PFS in PRRT patients with more extensive disease. Finally, our institution is a tertiary referral center, and some of our patients were followed up in their local hospitals. In some cases, it was difficult to retrieve patient follow-up information despite best efforts.

CONCLUSION

^{177}Lu-DOTATATE PRRT appears to be generally safe in NET patients with preexisting CKD 3. We found a low incidence of

grade 3 or 4 hematologic toxicity (9%) and permanent major nephrotoxicity (3%). The average annual eGFR loss was estimated at 2.5%. We found no significant risk factors for development of reduced renal function. In our cohort of CKD 3 NET patients, ^{177}Lu DOTATATE PRRT appears to have a good therapeutic effect, with PFS of 42 mo and overall survival of 47 mo. Most patients also had an improved quality of life.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What are the efficacy and safety of ^{177}Lu-DOTATATE in patients with NETs and reduced renal function—that is, an eGFR below 60 mL/min/1.73 m^2?

PERTINENT FINDINGS: In this single-center retrospective analysis of 33 NET patients, a permanent reduction of more than 10% in eGFR of any grade was recorded in 45% of patients, with 1 patient (3%) developing grade 4 nephrotoxicity. No significant relationship was found between renal risk factors and a permanent reduction in renal function.

IMPLICATIONS FOR PATIENT CARE: There is a low incidence of grade 3 or 4 renal toxicity with ^{177}Lu-DOTATATE; therefore, patients with CKD 3 could be considered for treatment with ^{177}Lu-DOTATATE.

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