

# Evaluation of Liver and Renal Toxicity in Peptide Receptor Radionuclide Therapy for Somatostatin Receptor Expressing Tumors: A 2-Year Follow-Up

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## Abstract

**Background:** Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin receptor (SSR) analogs is now an established systemic treatment for neuroendocrine tumors (NET). However, more short- and long-term data about renal and hepatotoxicity is needed. Here we present our experience in this clinical scenario.

**Methods:** Eighty-six patients with progressive SSR-expressing malignancies underwent PRRT with Lu-177 Dotatate and were followed up for up to 2 years. Laboratory tests were done 1 week before each cycle and every 2 months at follow-up. Hepatic and renal toxicity was determined based on NCI CTCAE V5.0.

**Results:** 55/86 (64%) patients completed all 4 cycles of PRRT; 18/86 (20.9%) are currently being treated; 13/86 (15.1%) had to discontinue PRRT: 4/13 (31%) due to hematologic toxicity, 9/13 (69%) due to non-PRRT-related comorbidities. Out of the patients who finished treatment, only transient grade 2 toxicities were observed during PRRT: hypoalbuminemia in 5.5% (3/55), and renal toxicity (serum creatinine and estimated glomerular filtration rate) in 1.8% (1/55). No grade 3 or 4 liver and renal toxicity occurred. Patients presenting with impaired liver or renal function prior to PRRT, either improved or had stable findings. No deterioration was observed.

**Conclusion:** Peptide receptor radionuclide therapy does not have a negative impact on liver and renal function, even in patients with pre-existing impaired parameters. No grade 3 or 4 hepatic or renal toxicity was identified. Only transient grade 2 hypoalbuminemia in 5.5% and nephrotoxicity in 1.8% of patients were seen during PRRT.

**Key words:** renal toxicity; hepatotoxicity; peptide receptor radionuclide therapy; neuroendocrine tumors; Lu-177 dotatate.

## Implications for Practice

Our findings show that peptide receptor radionuclide therapy (PRRT) is a safe treatment for liver and renal function, even in patients with pre-existing impaired liver and renal parameters. This might aid in expanding the current cutoff values as criteria to receive PRRT so that treatment is not withheld from patients who need it.

## Introduction

The majority of neuroendocrine tumors (NET) overexpress somatostatin receptors (SSR) on their cell surface.<sup>1</sup> Somatostatin analogs (SSA) were developed to target these receptors and lead not only to symptomatic relief in functioning NET but also have an antiproliferative effect.<sup>2,3</sup> Somatostatin receptors are the target for molecular imaging and targeted radionuclide therapies. The SSA Dotatate can be labeled with the positron emitter gallium-68 (Ga-68) for imaging with positron emission tomography (PET), and with the  $\beta$ -emitter lutetium-177 (Lu-177) for treatment.<sup>4,5</sup> Peptide receptor radionuclide therapy (PRRT) is a targeted systemic treatment option for metastatic NET.<sup>6</sup> Peptide receptor radionuclide therapy is known to have

a safe profile with little side effects.<sup>7</sup> Renal failure due to radiation-induced inflammation and fibrosis of the kidneys has been reported, especially when using yttrium-90 (Y-90), but less since the introduction of nephroprotection with amino acids.<sup>7</sup> Reported hepatotoxicity range from low<sup>8,9</sup> to high.<sup>10</sup> However, there are only a few studies dedicated to liver toxicity of PRRT, and especially studies reporting on long-term effects are lacking. It is important to understand PRRT-related toxicities, especially in patients with pre-existing impaired renal or liver function and to understand the time of occurrence and its possible chronicity. We therefore aimed to assess renal and liver radiotoxicity after 4 cycles of PRRT in patients with unresectable, progressive SSR-positive malignancies, with or without renal/hepatic

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functional impairment before PRRT, with a follow-up of up to 2 years.

## Material and Methods

### Participants

Patients treated with Lu-177 Dotatate from May 2018 to September 2020 (mean follow-up time  $11.6 \pm 7.1$  (range 7-26) months) were included. All patients had inoperable, metastasized and progressive SSR-positive malignancies, assessed by anatomical imaging (contrast enhanced computed tomography [CT] and/or magnetic resonance imaging [MRI]), and molecular imaging (Ga-68 Dotatate PET/CT or PET/MRI). All tumors were histologically verified.

This cohort included G1 and G2 NET, as well as SSR-expressing well-differentiated G3 NET. Patient characteristics and relevant clinical data including laboratory parameters before and after PRRT were analyzed.

This retrospective review was approved by the local Institutional Review Board and a waiver of informed consent was granted.

### Treatment Protocol

All patients received PRRT with Lu-177 Dotatate (Lu-177-DOTA0-Tyr3-Octreotate; Lutathera; Advanced Accelerator Applications, NJ, USA). The treatment protocol consisted of an antiemetic (ondansetron 8 mg) given intravenously (i.v.) to avoid potential nausea from nephroprotection, followed by nephroprotective infusion of amino acids (25 g lysine and 25 g arginine in 1 L sterile water). Once 250 cc of amino acids had been administered, Lu-177 Dotatate was simultaneously infused through a different i.v. access over 30 minutes. Thereafter, the nephroprotective amino acid infusion continued for a total of 2 L. Seven thousand four hundred megabecquerels (200 mCi) of Lu-177 Dotatate were administered for each cycle every 8 weeks for a total of 4 cycles. To avoid interference with binding at the SSR, long-acting octreotide injections were held for 1 month and short-acting octreotide for at least 24 hours prior to Lu-177 Dotatate administration.

### Safety Assessment

Before PRRT, patients' history, anatomical and molecular imaging, as well as hepatic, renal and bone marrow reserve parameters were reviewed to assess treatment eligibility. The patients had laboratory tests done 1 week prior to each cycle and every 2 months at follow-up to evaluate toxicities. The laboratory tests included: serum albumin, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, and estimated glomerular filtration rate (eGFR). The inclusion criteria for PRRT at our institution were based on the NETTER-1 clinical trial, the standard procedure for PRRT by the North American Neuroendocrine Tumor Society and the Society of Nuclear Medicine and Molecular Imaging, as well as Lutathera package insert (for hepatic and renal parameters: total bilirubin  $\leq 3 \times$  upper limit normal; serum albumin  $> 3$  g/dL; serum creatinine  $< 1.7$  mg/dL or eGFR  $> 50$  mL/minute/1.73 m<sup>2</sup>). However, exemptions were made in specific cases considering the overall benefit for the patient.

Toxicity was determined based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0.

### Imaging

Pre-treatment imaging with Ga-68 Dotatate PET/computed tomography (CT) or PET/magnetic resonance imaging (MRI) was performed to assess SSR positivity. Liver tumor burden was categorized as: none ( $< 10$  metastases), high ( $> 10$  metastases), bulky disease and diffuse liver infiltration (no individual lesions). Pre-existing ascites was noted. Further molecular imaging was obtained after 2 cycles and 4-6 weeks after completion of PRRT. Follow-up imaging every 3 months was done with either CT, MRI and/or PET.

### Statistical Analysis

All data were registered in a structured database. Descriptive statistics were performed using Microsoft Excel for Mac, version 16.35. Continuous data are presented as mean  $\pm$  SD, range minimum (min)-maximum (max) values.

### Results

Eighty-six patients (42 women and 44 men,  $63.3 \pm 10.4$  [range 37-81] years old) underwent PRRT with Lu-177 Dotatate. Eighty had progressing NET (40 pancreatic, 27 small intestine, 1 cecum, 1 appendix, 1 gastric, 3 atypical lung, and 7 of unknown primary), 4 had paraganglioma and 2 had pheochromocytoma.

To assess the radiation effect of PRRT on liver and kidney function, we evaluated the patients who finished all 4 cycles of treatment. 55/86 (64%) patients completed PRRT by September 2020, receiving a full dose of 7400 MBq (200 mCi)/cycle except for one patient who received a one-time reduced dose of 3700 MBq (100 mCi) due to hematologic toxicity. 18/86 (21%) continue to receive treatment. 13/86 (15%) patients did not finish all 4 cycles: 4/13 due to hematologic toxicity, and 9/13 due to non-PRRT related comorbidities (ie, stroke, sepsis, and peritonitis).

The mean number of prior treatments in our cohort was  $3.4 \pm 1.4$  (range 1-7) and included SSA, surgery, chemotherapy, mTOR kinase inhibitors, immunotherapy, radiation, and liver-directed therapies (LDT).

### Liver Toxicity

Overall, 15/55 (27.3%) patients demonstrated hepatotoxicity, expressed either in one or multiple hepatic parameters of grade 1 or 2 toxicity. Table 1 summarizes all patients showing liver toxicity.

Liver tumor burden before PRRT was diffuse (no individual lesions) in 1/55 (1.8%), widespread in 30/55 (54.5%), high ( $> 10$  liver metastases) in 11/55 (20%), low ( $< 10$  liver metastases) in 5/55 (9.1%) and not detectable in 8/55 (14.6%) patients. Baseline ascites was seen in 5/55 (9.1%) and 22/55 (40%) patients had previous LDT.

When stratified to their liver tumor burden at baseline, all patients demonstrating grade 2 liver toxicity had widespread disease, history of TACE and 2/3 (66.7%) presented with ascites at baseline. Table 2 summarizes these participants.

No long-term liver toxicities related to PRRT were identified in our population. Short-term toxicities were as follows:

### Serum Albumin

No patient demonstrated grade 3 or 4 hypoalbuminemia.

42/55 (82%) patients presented with normal albumin levels at baseline: 2/42 patients developed toxicity grade 2, whereas no follow-up data were available in one patient as he passed

away 1 month after completion of PRRT due to small bowel obstruction and the other patient's toxicity was considered unrelated to PRRT as he had concurrent fungemia-related acute renal failure and albumin recovered to normal levels after antifungal treatment.

13/55 (24%) patients presented with abnormal albumin level at baseline: 2/13 patients developed grade 2 toxicity at last cycle and recovered to initial levels. Both patients had previous LDT and baseline ascites. One patient presented with borderline albumin for PRRT (2.9 g/dL) which recovered after first cycle and stayed within normal range thereafter.

**Total Bilirubin**

No patient demonstrated grade 3 or 4 hyperbilirubinemia.

50/55 (90%) patients showed normal bilirubin at baseline: 1/50 developed grade 2 toxicity at cycle 4 and recovered to normal levels 3 months later. This patient had previous LDT and ascites at baseline.

3/55 (5%) patients had abnormal bilirubin at baseline. One-third patients with significant liver disease burden developed hyperbilirubinemia grade 3 and ascites 14 months after the first PRRT cycle, concerning for disease progression. As hyperbilirubinemia recovered after chemotherapy was initiated, this toxicity was considered to be related to disease progression (Fig. 1). Two-thirds patients presenting with abnormal bilirubin recovered to normal levels during PRRT.

Improvement of total bilirubin was seen in two-third patients: both patients presented with borderline

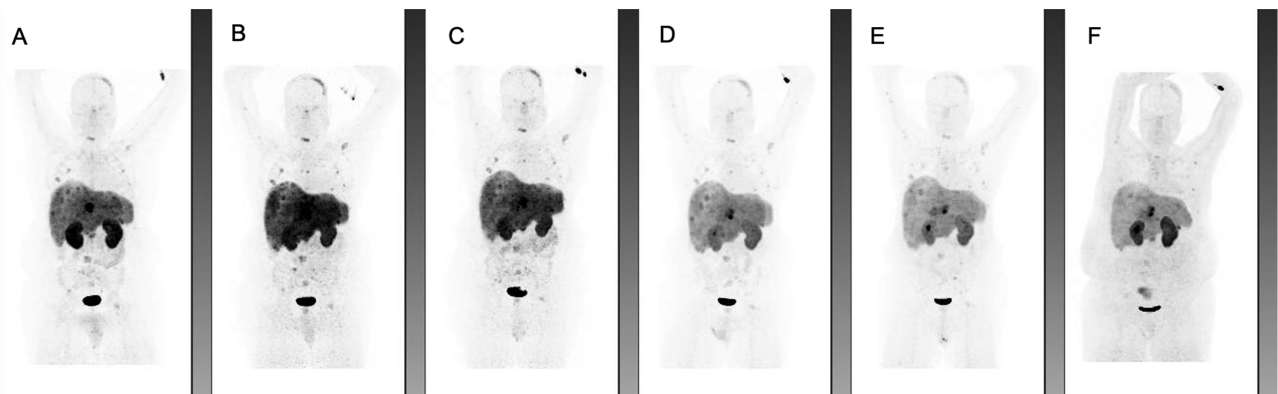
**Table 1.** Distribution of PRRT-induced hepatotoxicity.

	Baseline	Grade 1	Grade 2	Grade 3	Grade 4	Total	Liver directed therapy	Ascites at baseline
Albumin N=3	Normal	0	1	0	0	1	1	1
	Abnormal	0	2	0	0	2	2	2
Bilirubin N=2	Normal	1	1	0	0	2	1	1
	Abnormal	0	0	0	0	0	0	0
ALP N=3	Normal	3	0	0	0	3	2	1
	Abnormal	0	0	0	0	0	0	0
AST N=3	Normal	3	0	0	0	3	1	0
	Abnormal	0	0	0	0	0	0	0
ALT N=7	Normal	6	0	0	0	6	3	1
	Abnormal	0	1	0	0	1	1	0

All toxicities were short-term and transient.

**Table 2.** All patients developing grade 2 hepatotoxicity, N = 3.

Patient	Primary tumor	Liver tumor burden	Ascites	Prior liver-directed therapy	Lines of prior therapies	PRRT-induced toxicity
1	Pancreas	Widespread	Ascites	TACE	5	Grade 2 short term
2	Pancreas	Widespread	none	TACE (4x)	5	Grade 2 short term
3	Small intestine	Widespread	Ascites	SIRT (2x), TACE	4	Grade 2 short term



**Figure 1.** Forty-nine-year-old man with G2 small bowel NET presenting with hyperbilirubinemia (1.5 mg/dL) and elevated aminotransferases at baseline. Maximal intensity projection (MIP) images from Ga-68 Dotatate PET at baseline: diffuse metastatic infiltration of the whole liver and multiple bone lesions (A), after 2 cycles: stable disease (B), after completion of PRRT: stable disease (C), 4 months after PRRT: stable disease (D), 7 months after PRRT: stable disease but ascites with sudden increase of bilirubin to 5.5 mg/dL and carcinoid symptomatology, concerning for disease progression (E), 10 months after PRRT and 3 months after chemotherapy: stable disease with progressing ascites; symptomatology and bilirubin improved (F).

hyperbilirubinemia of 1.3 mg/dL at baseline, which improved to normal range after cycles 1 and 3, respectively.

### Alkaline Phosphatase

No grade 2, 3, or 4 toxicity was observed for ALP.

29/55 (53%) patients presented with normal ALP at baseline. 3/29 patients developed toxicity grade 1 after cycle 1 and recovered after PRRT.

26/55 patients (47%) patients presented with elevated ALP at baseline, whereas 23/26 patients had remained at initial levels throughout PRRT and follow-up and 3/26 patients improved, however not within in the normal range (Fig. 2).

### Aspartate Aminotransferase

No patient demonstrated grade 2, 3, or 4 toxicity secondary to PRRT.

41/55 (75%) patients presented within normal range at baseline. 3/41 patients developed grade 1 toxicity after the first cycle, and recovered either during PRRT or within 5-months follow-up.

14/55 (25%) patients presented within abnormal range at baseline. No PRRT-induced toxicity was developed.

### Alanine Aminotransferase

No patient demonstrated grade 3 or 4 toxicity secondary to PRRT.

43/55 (78%) patients presented within normal range at baseline. 6/43 patients developed grade 1 toxicity during PRRT whereas 4/6 patients recovered during follow-up and 2/6 patients remained with a grade 1 toxicity during follow-up.

12/55 (22%) patients presented with abnormal levels at baseline, whereas 9/12 patients remained at baseline levels during PRRT and follow-up, and 3/12 patients improved to normal range and remained during PRRT and follow-up.

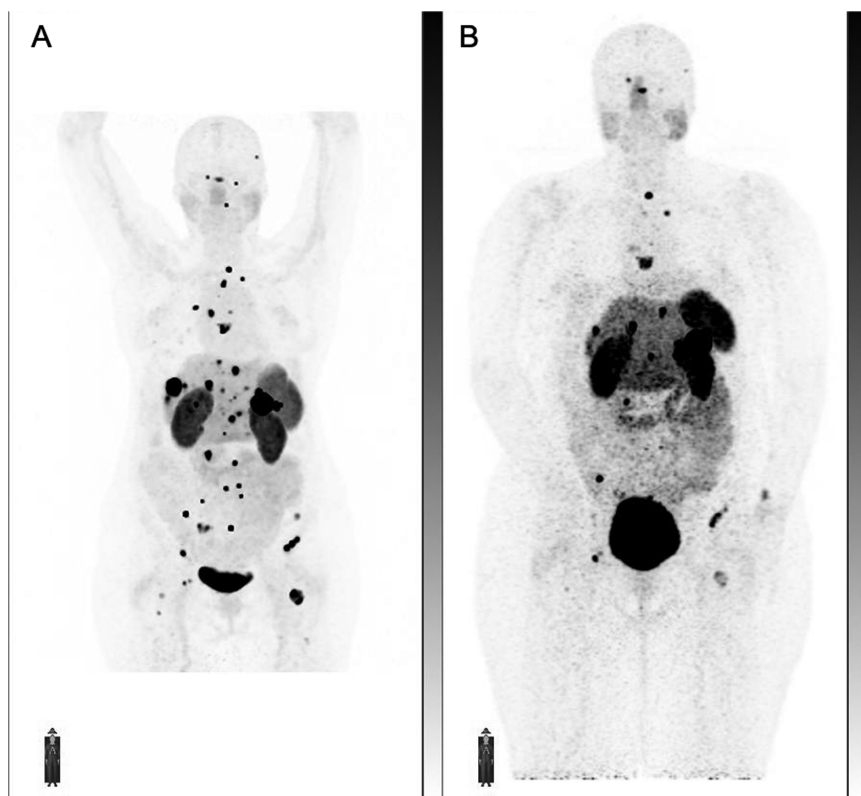
### Renal Toxicity

Overall, 7/55 (12.7%) patients showed nephrotoxicity, expressed in elevated creatinine and decreased eGFR, grade 1 or 2. Table 3 summarizes all patients showing nephrotoxicity. Four patients with known chronic kidney disease (CKD) were treated, whereas 3 showed no deterioration of creatinine nor eGFR after PRRT and 1 developed borderline grade 2 toxicity. Fig. 3 shows creatinine development of patients with CKD.

### Creatinine

No patient demonstrated any grade 3 or 4 PRRT-induced toxicity.

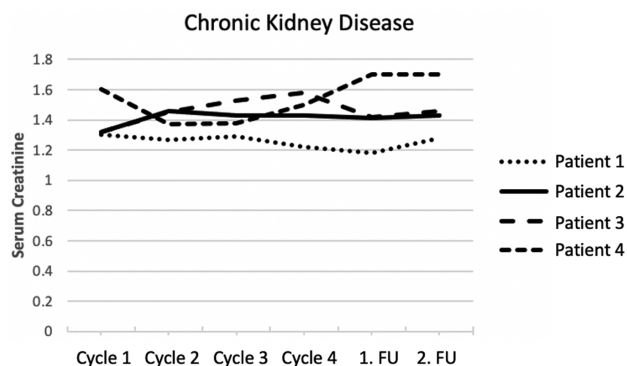
47/55 (85.5%) patients presented with normal creatinine at baseline: 6/47 (12.8%) patients developed grade 1 toxicity during PRRT which resolved in all patients 2-4 months after treatment.



**Figure 2.** Sixty-seven-year-old woman with G2 NET of unknown origin and status post TACE twice, presented for PRRT with elevated ALP (460 U/L). She developed transient grade 1 toxicity (elevated AST and ALT) during treatment. Aspartate aminotransferase and ALT recovered 6 months after last PRRT cycle. Maximal intensity projection images from Ga-68 Dotatate PET prior to PRRT: multiple hepatic, osseous, mediastinal, and retroperitoneal lymph node metastases (A), and 8 months after completion of PRRT: treatment response with decreased number, size, and avidity of known metastases (B).

**Table 3.** All PRRT-related renal toxicity based on creatinine, *N* = 7

Renal function at baseline	Grade 1	Grade 2	Grade 3	Grade 4	Total	Recovery
Normal	6	0	0	0	6	Yes
Abnormal	0	1	0	0	1	Yes

**Figure 3.** Creatinine development during PRRT and follow-up in patients with CKD (*n* = 4).

8/55 (14.5%) patients presented with abnormal creatinine at baseline, whereas 7/8 patients remained within this range during PRRT and follow-up, 1/8 patients with known CKD developed borderline grade 2 toxicity at third cycle but recovered to normal range 3 months after completion of PRRT.

## Discussion

Peptide Receptor Radionuclide Therapy with Lu-177 Dotatate is an established systemic treatment for unresectable, metastatic, and SSR-overexpressing malignancies. Hematotoxicity and renal toxicity due to PRRT have been previously reported and are considered mild.<sup>7,8</sup> However, little remains known about possible short- and long-term adverse effects of PRRT on liver function. Neuroendocrine tumor patients may present with widespread, bulky disease in the liver, which is the main determinant for morbidity and mortality.<sup>11</sup> Reported hepatotoxicity ranges from low<sup>8,9</sup> to very high.<sup>10</sup>

In our heterogeneous cohort of NET patients, no grade 3 or 4 liver toxicities related to PRRT were identified. A total of 3/55 (5.5%) patients developed grade 2 hypoalbuminemia and recovered at follow-up. Abnormal liver parameters at baseline seemed to not predispose to PRRT-induced liver toxicity. This finding questions the need for a cutoff level for hepatic laboratory data as criteria to receive PRRT.

All patients developing grade 2 hepatotoxicity had prior TACE. The cumulative damage to the liver plays a central role in determining toxicity as TACE lead to hepatocellular apoptosis and peribiliary fibrosis.<sup>12</sup> This might indicate that previous liver-directed therapies could be a predictor for PRRT-induced liver toxicity. Patients demonstrating hepatotoxicity also showed widespread hepatic tumor burden with 67% presenting with ascites, as a sign of impaired liver function, at baseline. Data comparing tumor burden and hepatotoxicity were limited. One study showed similar results in only 1 patient.<sup>13</sup> Recently, a post hoc analysis of the NETTER-1 clinical trial comparing liver tumor burden with outcome

showed that grades 3 and 4 hepatotoxicity were rare and not correlated with high liver tumor burden prior to PRRT.<sup>14</sup> However, the combination of previous LDT, widespread liver metastases and ascites seems to be a strong predictor for developing hepatotoxicity, albeit transient in nature.

Riff et al<sup>10</sup> published the only paper dedicated to hepatotoxicity of PRRT. They compared liver toxicity of PRRT with standard of care treatment in 100 patients, respectively. Hepatotoxicity was high in the PRRT cohort with 59% when compared with standard of care with 31% and consisted of 29% hyperbilirubinemia and 41% ascites. However, these patients had various amounts of treatment cycles with either Y-90, In-111, or Lu-177 Dotatoc treated in different European centers at a time when PRRT was not available in the US. Y-90 has been reported to result in more adverse events compared with Lu-177 Dotatate.<sup>15</sup> In our study, we did not observe such a high rate of hepatotoxicity, which could be related to patients treated consecutively without waiting time and consistently with Lu-177 Dotatate. However, consistent with our findings, underlying or development of ascites seems to be a predictor of hepatotoxicity.

Renal toxicity in PRRT decreased significantly after the introduction of nephroprotective arginine and lysine amino acid infusion and switch to Lu-177 labeled compounds. Grades 3 and 4 nephrotoxicity have been reported low with <2%.<sup>7,16</sup> We did not observe any grade 3 or 4 renal toxicity. Borderline grade 2 elevated creatinine was observed in 1.8% which is similar to previously published studies.<sup>8,15</sup> Importantly, our data show that 75% patients with CKD did not express worsening renal function after PRRT. This indicates that there is room to treat beyond the current cutoff value for creatinine; however, larger studies with a longer follow-up time are needed.

Limitations of this study are the small, heterogeneous patient population including various types of NET (G1-G3), paraganglioma and pheochromocytoma, and the relatively short follow-up.

## Conclusion

Peptide receptor radionuclide therapy is a safe treatment for liver and renal function, even in patients with pre-existing impaired liver and renal parameters. The only grade 2 liver toxicity observed was early transient hypoalbuminemia in 5.5%. Borderline grade 2 nephrotoxicity was observed in 1 patient with CKD. No grade 3 or 4 hepatic or renal toxicity was identified. These findings question the need for a definite cutoff level for hepatic laboratory data as criteria to receive PRRT.

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## Conflict of Interest

The authors indicated no financial relationships.

## Author Contributions

Conception/design: H.D., V.F., G.A.F., S.S., G.A.D., A.I., C.M.A. Provision of study material or patients: H.D., V.F., G.A.F., S.S., G.A.D., A.I., C.M.A. Collection and/or assembly

of data: H.D., V.F., G.A.F., S.S., G.A.D., A.I., C.M.A. Data analysis and interpretation: H.D., V.F., G.A.F., S.S., G.A.D., A.I., C.M.A. Manuscript writing: H.D., V.F., G.A.F., S.S., G.A.D., A.I., C.M.A. Final approval of manuscript: H.D., V.F., G.A.F., S.S., G.A.D., A.I., C.M.A.

## Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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