Journal of Nuclear Medicine, published on April 20, 2023 as doi:10.2967/jnumed.122.264533

Evaluation of Hepatotoxicity from Peptide Receptor Radionuclide Therapy in Patients with Gastroenteropancreatic Neuroendocrine Tumors and a Very High Liver Tumor Burden

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The aim of the current study was to describe the risk of hepatotoxicity for patients with gastroenteropancreatic neuroendocrine tumors undergoing peptide receptor radionuclide therapy (PRRT) with a very high liver tumor burden, defined as tumor involving more than 75% of the liver. **Methods:** We conducted a retrospective analysis of 371 patients who received at least 1 cycle of ^{177}Lu-DOTATATE at Mayo Clinic for advanced gastroenteropancreatic neuroendocrine tumors. We identified 15 total patients with more than 75% liver involvement on ^{68}Ga-DOTATATE PET/CT and with either a contrast-enhanced abdominal MRI or dual-phase abdominal CT examination. **Results:** Of the 15 patients with more than 75% liver involvement, 1 experienced hepatotoxicity (i.e., worsening liver enzymes or bilirubin) as defined by the Common Terminology Criteria for Adverse Events, version 5.0. No patients had grade 3–5 hepatotoxicity (i.e., clinical signs of liver failure). **Conclusion:** When considering the risk of liver injury from PRRT due to burden of disease, our data suggest that PRRT may be a safe option in patients with more than 75% liver involvement. Future efforts should be made to determine the safety profile of PRRT in patients with varying degrees of liver involvement.

Key Words: gastrointestinal; neuroendocrine; peptides; hepatic; neuroendocrine tumor; peptide receptor radionuclide therapy

J Nucl Med 2023; 64:1–5
DOI: 10.2967/jnumed.122.264533

Neuroendocrine tumors (NETs) constitute a heterogeneous group of tumors arising from neuroendocrine cells. They can originate in any organ that has neuroendocrine cells but most commonly are in the pulmonary system and the gastrointestinal tract. The liver is the most common distant site of metastasis in patients with gastroenteropancreatic NETs and is also the main site of organ involvement leading to morbidity and mortality (*1*). Liver tumor burden is also a consideration when determining patient candidacy for peptide receptor radionuclide therapy (PRRT). Although there is concern about an increased risk of radiation-induced hepatitis with increasing liver involvement, PRRT with ^{177}Lu-DOTATATE has been shown to be both safe and effective in patients with more than 50% liver involvement, with no difference in progression-free survival (*2*). However, it is unclear whether PRRT is safe in patients with a very high liver tumor involvement, namely, in those for whom the liver appears to be mostly replaced by metastatic tumor.

PPRT is a paradigm-shifting treatment for gastroenteropancreatic NETs, especially since the publication of the NETTER-1 trial on patients with small-bowel NETs (*2*). Although no randomized trials of PRRT in patients with pancreatic NETs have yet been reported, there is an abundance of evidence suggesting efficacy in that patient cohort, which comprises the second largest subgroup of patients with gastroenteropancreatic NETs (*3*). ^{177}Lu-DOTATATE has been rapidly adopted as a treatment modality in the United States since its approval by the Food and Drug Administration in January 2018. PRRT works by binding to the somatostatin receptor, most commonly somatostatin receptor 2, on the surface of the NET cell. This allows for the discriminative delivery of a payload (i.e., radionuclide). ^{177}Lu-DOTATATE emits β- and γ-radiation causing single-stranded DNA breaks within the cell (*4,5*). The more common toxicities that have been discovered in relation to PRRT include nephrotoxicity, myelosuppression, and hepatotoxicity (*6–11*). Although there is a hypothetical concern about an increased risk of radiation-induced hepatitis in patients with increasing liver involvement, PRRT with ^{177}Lu-DOTATATE has been shown to be both safe and effective in those with less than 25%, 25%–50%, and more than 50% liver involvement, with no significant differences in progression-free survival or rates of hepatotoxicity despite varying rates of tumor burden (*7*). It is worth questioning whether the gradient of liver involvement, for example more than 75% involvement, would still have similar outcomes to more than 50%. Thus, it remains unknown whether PRRT is safe in patients with a very high liver tumor involvement, namely, in those for whom the liver appears to be mostly replaced by metastatic tumor. The aim of this study was to assess and describe the risk of hepatotoxicity from PRRT in NET patients with more than 75% liver involvement.

MATERIALS AND METHODS

The institutional review board approved this retrospective study, and the requirement to obtain informed consent was waived. We then conducted a retrospective analysis of 371 patients who received at least 1 cycle of PRRT at 1 of the 3 Mayo Clinic sites (Minnesota, Florida,

Received Jun. 16, 2022; revision accepted Feb. 7, 2023.
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Published online ▪▪▪▪▪▪▪▪▪▪▪▪▪▪.

or Arizona). As a screening tool, we performed a refined search for "innumerable liver metastasis" within either the ^{68}Ga-DOTATATE PET/CT or contrast-enhanced abdominal MRI or CT imaging report. We used this search term to identify potential candidates with permeative or extensive hepatic metastatic disease that compromised most of the physiologic liver parenchyma. Although we did not specifically try to identify patients with bulky oligometastatic hepatic disease that could in theory replace large portions of the liver parenchyma, this presentation is much less common (*12*). We identified 22 potential patients with more than 75% liver metastatic involvement based on clinical reports, and subsequently, 3 independent reviewers confirmed a total of 15 patients with more than 75% liver involvement as identified on ^{68}Ga-DOTATATE PET/CT and either diagnostic contrast-enhanced MRI or CT. Baseline laboratory values were obtained within 1 mo before the initiation of PRRT. Post-PRRT laboratory values were determined as the highest recorded values anywhere from the start of PRRT to 3 mo after the completion of therapy. Ascites as a complication of PRRT was defined as any reading of ascites on imaging after at least 1 cycle of PRRT in a patient who did not previously show ascites on any formal imaging. Hepatotoxicity was defined as any change in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin that was grade 2 or higher according to the Common Terminology Criteria for Adverse Events, version 5.0. The time to follow-up was calculated from the start of PRRT to the date of each patient's last follow-up appointment.

Selection of Regions of Interest

To determine that more than 75% of liver had been replaced by hepatic metastatic disease, ^{68}Ga-DOTATATE PET images were coregistered to either T1-weighted contrast-enhanced sequences of the corresponding MRI of the liver (8/15) or contrast-enhanced CT (7/15) if MRI was not available. A board-certified radiologist using the Absolute Threshold Contouring Tool (MIM Software) drew regions of interest over the enhancing tumors and entire liver to calculate a preliminary percentage of tumor involvement of the liver. Metabolically active somatostatin-expressing hepatic metastatic disease was then confirmed in the enhancing lesions when the ^{68}Ga-DOTATATE SUV_{max} of the enhancing tumor was more than 2.0 times that of the normal hepatic parenchyma. This ^{68}Ga-DOTATATE PET analysis was done to confirm that the enhancing lesions were also somatostatin-avid and thus likely to incorporate ^{177}Lu-DOTATATE at a rate greater than physiologic liver parenchyma. The SUV_{max} of normal hepatic parenchyma was identified by placing up to a 30-mm spheric region of interest over nonenhancing normal hepatic liver parenchyma, depending on the area of the uninvolved liver.

RESULTS

Demographics

In total, 15 patients were identified as having more than 75% liver involvement before initiation of PRRT. Patient demographics are described in Table 1. The median time to follow-up was 19.4 mo (range, 3.9–45.6 mo). The median age of the included patients was 62 y (range, 36–77 y), and most patients were male (11/15; 73%). The median Eastern Cooperative Oncology Group performance status for all patients was 1 (range, 0–2) before PRRT. The primary site of disease was the small bowel (9/15; 60%), and most patients had World Health Organization grade 2 tumors (9/15; 60%) (*13*). Before the initiation of PRRT, 6 of 15 (40%) patients had grade 1 elevation in alkaline phosphatase levels at baseline. One of these 6 patients had a concomitant grade 1 elevation in aspartate transaminase and alanine transaminase levels (Table 2). Additionally, 3 of 15 (20%) patients had a grade 3 elevation in alkaline phosphatase. Ascites was present on abdominal imaging in 5 of 15 (33%) patients: 3 patients had grade 1 ascites, and 2 patients had grade 2 ascites. In 1 of 15 patients, hepatic miliary disease was noted on ^{68}Ga DOTATATE PET/CT and MRI (Figs. 1A–1D). Regarding concomitant medication use, 9 of 15 patients were deemed as taking potentially hepatotoxic medications: 6 were taking acetaminophen as needed for pain, 2 were taking moderate-intensity statin medications, and 1 was taking allopurinol.

TABLE 1
Patient Demographics

Demographic	Data
Total patients	15
Mean age (y)	62
Sex	
Male	11 (73%)
Female	4 (27%)
Primary site of disease	
Small bowel	9
Pancreas	5
Unknown	1
World Health Organization tumor grade	
1	4
2	9
3	1
Unknown	1

Data are *n,* except for age.

Hepatotoxicity

After PRRT, in 1 of 15 (6%) patients we identified hepatotoxicity, which we defined as any change in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin of grade 2 or higher according to the Common Terminology Criteria for Adverse Events, version 5.0 (Table 2). This patient experienced grade 2 hyperbilirubinemia. Grade 1 hepatoxicity was also discovered in 5 of 15 (53%) patients, with 4 of these patients having a grade 1 elevation in alkaline phosphatase levels alone and 1 of these patients also having a concomitant grade 1 elevation in aspartate aminotransferase. No patients in our review experienced grade 3–5 hepatotoxicity. Grade 1 ascites was noted in 3 of 15 (33%) patients and was not present before therapy, but none of these cases of ascites occurred in the setting of fulminant hepatic failure. All 3 cases of ascites appeared to be secondary to disease progression rather than a complication of PRRT. Albumin and international normalized ratios were also monitored during and after therapy, and no patients experienced adverse events in relation to these 2 indices. Interestingly, the patient who had miliary spread of hepatic disease did not experience significant hepatotoxicity as a complication of therapy.

Hematologic Toxicity, Nephrotoxicity, and Other Adverse Effects

Cytopenia (defined as grade 2 or above in the Common Terminology Criteria for Adverse Events, version 5.0) developed in 4 of 12 (33%) patients who did not have cytopenia present before treatment. Only 2 of these patients had grade 3 toxicity. One of these 4 patients had a gastrointestinal bleed in the setting of PRRT-induced cytopenia.

TABLE 2
Pre-PRRT and Post-PRRT Laboratory Values

Treatments before PRRT	Pre-PRRT laboratory values					No. of PRRT cycles	Post-PRRT laboratory values				
	AST	ALT	ALP	TBIL	Ascites		AST	ALT	ALP	TBIL	Ascites
Somatostatin analog	17	9	128	0.7	Y*	4	17	15	162*	0.3	Y
Somatostatin analog, everolimus	23	27	98	0.9	N	4	25	29	94	0.5	N
Somatostatin analog	24	23	81	0.4	N	4	34	44	138*	0.3	N
Somatostatin analog	27	24	84	0.4	N	3	46	18	114*	0.9	N
Somatostatin analog, everolimus	24	14	164	0.3	Y*	1	47	41	177	0.5	N
Somatostatin analog	16	12	134	0.3	N	4	25	13	111	0.5	Y*
Somatostatin analog	81	60	206	0.2	N	4	73	73	283	0.4	N
Somatostatin analog, everolimus	43	23	934	0.7	Y*	2	45	40	575	0.6	N
Somatostatin analog, everolimus	48	11	105	0.7	N	2	68*	19	151*	1.6†	Y*
Somatostatin analog, hepatic embolization	42	42	164	0.6	Y†	4	23	15	121	0.5	Y
None	95	114	723	1.2	N	4	107	124	685	1	N
Somatostatin analog, capecitabine	42	59	610	1.2	N	4	44	90	320	1.0	N
Somatostatin analog	27	25	170	0.3	N	4	27	24	224	0.6	Y*
Somatostatin analog, capecitabine	22	12	172	1	Y†	4	23	10	150	1.1	N
Somatostatin analog, everolimus	25	22	103	0.4	N	4	35	34	198*	0.3	N

*Grade 1 adverse event.
†Grade 2 adverse event.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; TBIL = total bilirubin.

Additionally, 2 of 15 patients (13%) developed grade 2 renal failure after PRRT. Symptomatically, 6 of 15 (40%) patients complained of fatigue and 1 of 15 (6%) complained of nausea or vomiting after PRRT therapy. One patient developed a small-bowel obstruction after initiation of PRRT. Another patient with metastatic carcinoid heart disease developed acute pericarditis after initiation of PRRT, but after treatment with nonsteroidal antiinflammatory drugs, the patient was safely able to continue additional PRRT. Eastern Cooperative Oncology Group performance status declined in only 1 patient (6%), whereas the performance status of the rest of the patients remained the same or improved after treatment.

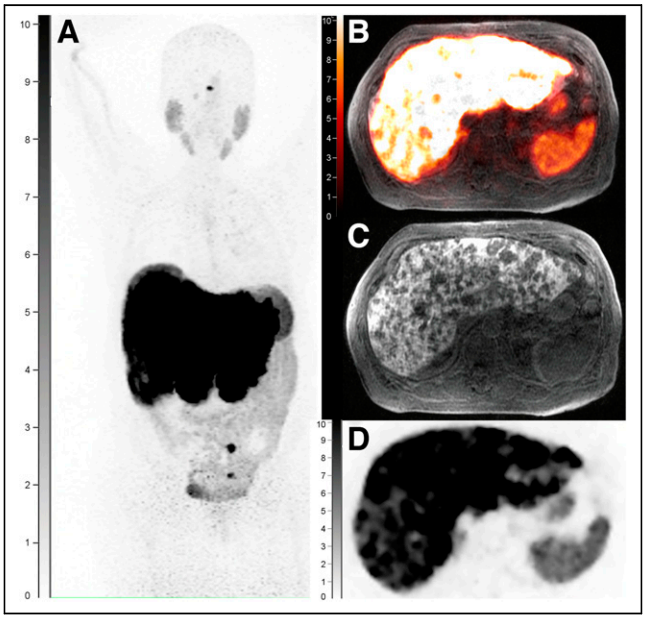

FIGURE 1. Miliary disease demonstrated on ^{68}Ga-DOTATATE PET/CT highlighting diffuse uptake in liver (PET maximum-intensity projection [MIP] [A], fused MRI/PET [B], and nonfused PET [D]) alongside T2 diffusion-weighted MRI of liver highlighting diffuse cancer involvement (MRI T2 diffusion-weighted image [C]). Scale = SUV.

Treatment Response and Survival

Overall, 4 of 15 patients completed fewer than 4 cycles of PRRT because of complications unrelated to hepatotoxicity: 1 experienced progressive disease, 1 developed severe renal failure, 1 developed cytopenia with infectious complications, and the last was still receiving PRRT at the time of analysis. Of those who had completed 4 cycles of PRRT (11/15; 73%) at the time of analysis, radiographic tumor response after therapy revealed improvement in 2 patients (18%), no change in 5 patients (45%), and progressive disease in 4 patients (36%). One patient had completed 3 cycles of PRRT and developed progressive disease. Two other patients had undergone only 2 cycles, and both experienced no change in radiographic tumor response. One patient has undergone just 1 cycle and has already demonstrated improvement. No patients died within 100 d of receiving PRRT. Five patients had died by the time of analysis. Among the 5 patients who died, the median time to death from the date of the last treatment with PRRT was 400 d (range, 100–619 d). Three patients died of progressive disease, 1 died of infection, and 1 died of renal failure.

DISCUSSION

Our retrospective review describes the largest analysis, to our knowledge, of patients with metastatic NETs who possessed a very high liver tumor burden (i.e., >75% involvement). Our results

suggest that PRRT may not pose a significant risk for hepatotoxicity in those with more than 75% liver involvement. Only 1 of 15 (6%) patients experienced a grade 2 or higher elevation in bilirubin level after PRRT with ^{177}Lu-DOTATATE. It remains indeterminate whether this patient experienced hepatoxicity in response to PRRT or disease progression. Previously, it has been shown that those with less than 25%, 25%–50%, and more than 50% hepatic involvement did not experience significant hepatotoxicity as a result of PRRT (*7*). A recent study suggested that pretreatment abnormalities of liver chemistries were associated with increased risk of PRRT cancellation, but that study did not address the liver tumor burden and safety of PRRT in patients with extensive liver metastases (*14*). Several studies have evaluated the estimated absorbed doses of organs and metastatic lesions of patients treated with ^{177}Lu-DOTATATE (*15–17*) and showed wide variation in the mean absorbed dose to tumor lesions, with sample reported average doses of 4.79 ± 4.23 Gy/GBq (*15*) and 3.85 ± 1.74 Gy/GBq (*18*). Our own unpublished data (August 2019) on a separate cohort of patients undergoing ^{177}Lu-DOTATATE, and who underwent same-day SPECT/CT to document uptake of ^{177}Lu-DOTATATE in the known metastatic disease, demonstrated a wide range of incorporation depending on the cycle of ^{177}Lu-DOTATATE treatment. Thus, because we did not perform prospective dosimetry on these patients, we did not attempt to retrospectively calculate an estimated radiation dose to the lesions and liver. Nonetheless, our laboratory and clinical findings support the notion that baseline liver tumor burden does not necessarily correlate with an increased risk for radiation-induced liver injury, even in patients with more than 75% liver involvement.

Although an increased rate of clinically overt hepatotoxicity (i.e., hepatic encephalopathy, ascites requiring intervention, and death from acute liver failure) has been previously reported in those receiving PRRT when compared with those receiving traditional NET therapy, details on hepatic tumor burden were lacking. For example, a retrospective analysis of 102 patients with pancreatic NETs treated with ^{177}Lu-DOTATATE found that a liver tumor burden of more than 50%, more than 1 line of chemotherapy, and an elevated level of alkaline phosphatase were independent risk factors for both progression and death, but only 1.0% of patients developed radiation hepatotoxicity from ^{177}Lu-DOTATATE (*19*). Several other retrospective studies of patients with NETs and documented metastatic liver disease treated with ^{177}Lu-DOTATATE found no cases of radiation-induced hepatotoxicity but also did not clearly document the degree of hepatic involvement (*20–22*). In our review, 3 patients developed new-onset ascites that was not present on formal abdominal imaging before PRRT, but each case reflected only grade 1 ascites and was likely attributable more to disease progression than to a complication of therapy. Moreover, no patients developed hepatic encephalopathy or acute liver failure or died within 100 d of treatment. Although 4 patients died from various causes, none died from treatment-associated liver failure. Although only 1 patient safely underwent radioembolization before PRRT, there may be an added hepatotoxic risk toward those who undergo previous radioembolization before PRRT (*7*).

Despite the availability of various radiopharmaceutical options for those with advanced gastroenteropancreatic NETs, all patients received ^{177}Lu-DOTATATE. This provides the highest affinity for somatostatin receptor 2–positive cells and undergoes renal clearance at an accelerated rate compared with other radiotherapies, such as ^{90}Y-DOTATOC, thereby decreasing the risks of bone marrow irradiation and nephrotoxicity (*23–26*). Although 42% of patients developed new cytopenias after PRRT, this rate represents no significant difference from the rate of cytopenias seen in traditional treatment modalities for metastatic NETs with liver involvement as reported elsewhere (*6,7*). Only 2 patients seemed to experience acute complications related to cytopenia: 1 patient experienced a gastrointestinal bleed, and another died of infectious complications. Although clinically significant nephrotoxicity after ^{177}Lu-DOTATATE PRRT is considered rare, 2 patients (13%) experienced renal failure after PRRT, consistent with previous reports (*6,7*). However, both were promptly seen and evaluated by nephrology specialists, and in neither case was the kidney injury attributed to the PRRT. One was thought to be secondary to dehydration compounded by renal oxalosis due to enteric hyperoxaluria after small-bowel resection for NETs. The second case demonstrated a resolution in estimated glomerular filtration rate seemingly overnight and was attributed to dehydration and the use of medications, including pseudoephedrine. Patients with progressive hepatic disease have reported a significantly improved quality of life in response to PRRT with ^{177}Lu-DOTATATE (*27*). In our own review, the Eastern Cooperative Oncology Group performance status remained the same or improved after PRRT in all but a single patient.

There are several limitations to the current review. In addition to the retrospective nature of the study, the primary limitation is the small sample size. Future directions should include validation of our results on a larger population with consideration of collaboration across multiple institutions. Future reproducibility incorporating the current methodology may also be limited given the subjective criteria for patients with more than 75% liver involvement as determined by 3 independent radiologists. Moreover, our study lacks information on the lesion and whole-liver dosimetry, which is an important factor to properly assess tumor burden.

CONCLUSION

When considering the risk of liver injury from PRRT due to burden of disease, our data suggest that PRRT may be a safe option even in patients with more than 75% liver involvement. Future studies should focus on stratifying patients according to the degree of liver involvement and volume of distribution (i.e., dosimetry). Moreover, efforts should be made to determine the safety profile on patients with an extremely high liver tumor burden.

DISCLOSURE

Jason Starr has received honoraria for consulting and serving on advertising boards for Ipsen, Advanced Accelerated Applications, Pfizer, Taiho, Tersera, Natera, Tempus, Cancer Expert Now, and Helsinn Therapeutics. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Is the risk of life-threatening hepatotoxicity from PRRT too great in NET patients with a liver tumor burden greater than 75%?

PERTINENT FINDINGS: Our retrospective cohort study of 15 patients showed that PRRT does not increase the risk of hepatotoxicity in this population.

IMPLICATIONS FOR PATIENT CARE: PRRT is likely a safe option even in patients with a very high liver tumor burden.

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