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REVIEW

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Peptide Receptor Radionuclide Therapy and the Treatment of Gastroentero-pancreatic Neuroendocrine Tumors: Current Findings and Future Perspectives

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Abstract

Purpose and Methods Patients with inoperable and metastasized neuroendocrine tumors (NETs), particularly those with grades 1 and 2, usually receive treatment with somatostatin analogues (SSAs). Peptide receptor radionuclide therapy (PRRT) has gained momentum over the past two decades in patients who progress on SSAs. 177Lu-DOTATATE is currently the most widely used radiopeptide for PRRT. We reviewed the recent evidence on PRRT and the treatment of gastroentero-pancreatic neuroendocrine tumors (GEP-NETs).

Results ^{177}Lu-DOTATATE can be used as neoadjuvant treatment in patients with inoperable GEP-NETs, who might be candidate for surgery after treatment and as adjuvant therapy after surgical intervention. Combination treatments of PRRT with chemotherapy or targeted agents as well as combinations of radionuclides in patients with NETs have been explored over the last few years. The majority of patients with NETs experience partial response or have disease stabilization, a small percentage has complete response, while some 30% of patients, however, will have disease progression. The safety and efficacy of retreatment with extra cycles of PRRT as salvage therapy have been evaluated in small retrospective series.

Conclusion Overall, there is evidence that disease control and quality of life improve significantly after 117Lu PRRT therapy. Clinical trials on this therapy are scarce, and there is a need for further studies to establish proper management guidelines.

Keywords Nuclear medicine · Theranostics · Lutetium · Neuroendocrine tumors · Peptide receptor radionuclide therapy

Introduction to NETs and Current Lines of Treatment

Neuroendocrine cells are distributed widely throughout the body. Neuroendocrine tumors (NETs), which are epithelial neoplasms with predominant neuroendocrine differentiation, can arise in most organs [1]. NETs are variable in their presentation and are divided into functioning tumors and nonfunctioning tumors. Functioning tumors produce peptide or amines that can cause distinct clinical symptoms such as flushing, diarrhea, hypoglycemia, gastric ulcers, or skin rash. Nonfunctioning tumors on the other hand are more common and usually present with a large mass or bleeding, and are somewhat difficult to differentiate from a classical cancer [2]. Even though clinical and pathologic features of these tumors are specific to the site of origin, some other characteristics are shared, regardless of site [1].

In the gastrointestinal system particularly, the most common malignant NETs arise from the midgut (henceforth the focus of this paper). For patients presenting with metastatic disease, the 5-year survival rate is less than 50% [3, 4]. Their classification was introduced by the European Neuroendocrine Tumor Society (ENETS) in 2006 and 2007 [5, 6], but an optimal cutoff value for the Ki-67 labeling index to distinguish different grades of gastroentero-pancreatic NETs (GEP-NETs) has not been conclusively established. However, the ENETS, American Joint Committee on Cancer (AJCC), and the 2010 WHO classification include a Ki-67 labeling cutoff of < 3% to define low-grade (G1), 3–20% for intermediate-grade (G2), and > 20% for high-grade (G3) NETs (Table 1) [5, 6].

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Table 1 ENETS/WHO nomenclature and classification for digestive system neuroendocrine tumors [1]

Differentiation	Grade	Mitotic count*	Ki-67 index+	Traditional	ENETS,WHO
Well-differentiated	Low grade (G1)	< 2 per 10 HPF	< 3%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 1
	Intermediate grade (G2)	2 to 20 per 10 HPF	3–20%	Carcinoid, atypical carcinoid$^{\Delta}$, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 2
Poorly differentiated	High grade (G3)	> 20 per 10 HPF	> 20%	Small cell carcinoma, large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, small cell

ENETS European Neuroendocrine Tumor Society, *WHO* World Health Organization

* Counted in 10 high-power fields (HPF). 10 HPF = 2 mm^2 , at least 40 fields (at ×400 magnification) evaluated in areas of highest mitotic density. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th edition

+ Ki-67 index as assessed by MIB1 antibody staining: percent positive after count of 2000 cells in area of highest nuclear labeling. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th edition

$^{\Delta}$ The term "atypical carcinoid" only applies to intermediate-grade NETs of the lung

If GEP-NETS are resectable, surgery is the primary approach. Patients with unresectable metastatic disease usually go through multiple lines of treatments including somatostatin analogue (SSA) therapy or targeted therapy, such as everolimus (mTOR inhibitor) or sunitinib (tyrosine kinase inhibitor) [7]. In patients with grade 1 and 2 NETs (Ki-7 LI of up to 20%) that are inoperable and metastatic, who have failed first-line somatostatin treatment, and whose tumors express high levels of somatostatin receptors (SSTRs), peptide receptor radionuclide therapy (PRRT) would be a viable option. PRRT usually involves DOTATOC, DOTATATE, and DOTANOC labeled either with ^{90}Y or ^{177}Lu [7]. Patients included in study protocols have positive NET histology and SSTR scintigraphy with ^{111}In OctreoScan or ^{68}Ga PET-Dota-peptide (Fig. 1). A positive scan denotes lesion uptake that is equal to or greater than the liver uptake [8]. Important criteria to be taken into account when considering PRRT include objective disease progression, adequate blood profile (hemoglobin, white cell, and platelet count levels), creatinine, and ECOG performance score ≤ 2 [8]. A good performance status means the patient would be self-sufficient and reduces the need for physical assistance during the treatment period (3 days/cycle). Recently published European Society for Medical Oncology (ESMO) Clinical Practice Guidelines have recommended PRRT up to the upper limit of Ki-67 LI to 30% [9]. Scintigraphic or PET tomoscintigraphic evaluation is to date the most accurate noninvasive method to identify and confirm the overexpression of functioning receptors [10]. An important issue in the consideration of PRRT is that the somatostatin receptors should be functional, i.e., able to internalize the receptor analogue complex and retain the radioactivity inside the cell. The critical issues for effective therapy are somatostatin receptor overexpression and the evidence of functionality. The nuclear physician can calculate a tumor-to-liver ratio as a relative measure of receptor number [11]; this ratio must be high for PRRT eligibility.

Mechanism of Action and Constituents of Radiolabeled SSAs

Somatostatin's actions include inhibiting hormone secretion, suppressing the release of insulin-like growth factors, inhibiting angiogenesis, and inducing apoptosis in the tumor tissue [12]. Such biologic effects are mediated through interaction with five subtypes of somatostatin receptors (SSTR1-5), which belong to the seven-transmembrane domain, G-protein-coupled receptor superfamily. The currently approved SSAs are octreotide and lanreotide, in slow-release formulations, long-acting release (LAR), and supersaturated solution (Autogel®).

Due to the overexpression of SSTRs in NETs, which is estimated to be in around 80% of NETs, they are considered suitable targets for PRRT with radiolabeled SSA. Once bound to their receptor, radiolabeled SSAs are internalized as per normal receptor recycling dynamics, and the breakdown products of the radiolabeled peptides are stored in lysosomes, thus enabling delivery and causing suspension of radioactivity inside the tumor cell [13]. This would result in radiation-induced DNA damage of the tumor cell and its eventual death.

Radiolabeled SSAs are made up of three main constituents; a radionuclide isotope, a ligand or carrier molecule (TOC or TATE), and a chelator or linker (DOTA) that binds them together and stabilizes the complex (Fig. 2). Chelators mainly used include DOTA (tetraazacyclododecane tetra-acetic acid) and DTPA (diethylenetriamine penta-acetic acid), while octreotide and octreotate (TOC and TATE, respectively) are generally used as ligands [14]. The most known and studied SSA is octreotide.

Three radionuclides (^{111}In, ^{90}Y, and ^{177}Lu) have been conjugated to SSAs (Table 2), and their different physical properties allow for specific benefits in radiation delivery [13]. Studies in the 1990s used high activities of the Auger electron-emitting [^{111}In-DTPA0]octreotide for PRRT.

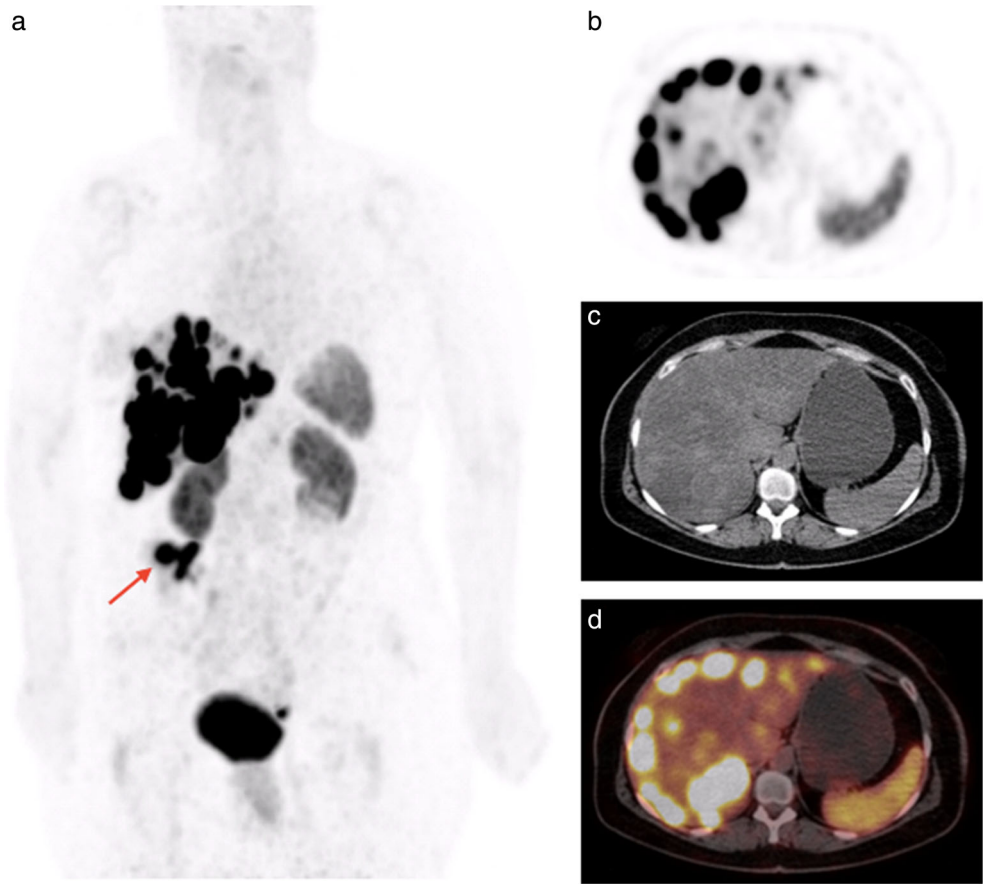

Fig. 1 **a** MIP image of ^{68}Ga DOTATOC PET shows the primary NET in the small bowel on the right side of the abdomen (red arrow) with extensive liver metastases, both demonstrating intense increased radiotracer uptake reflecting the high expression of the somatostatin receptors. The axial PET image (**b**), CT image (**c**), and fused PET/CT image (**d**) show the extensive liver metastases

Symptomatic relief was encountered in this therapy in patients with metastasized GEP-NETs. However, objective tumor responses were rare [15, 16]. The next generation of analogues used in PRRT consisted of [Tyr3]octreotide as a somatostatin analogue and DOTA as a chelator (instead of DTPA), which allows stable binding of the β-emitting radionuclide ^{90}Y. Its maximal tissue penetration is 12 mm and its half-life is 2.7 days. [^{90}Y-DOTA0,Tyr3]octreotide (^{90}Y-DOTATOC) was used in multiple phase I and phase II PRRT trials across several countries [17–24], with reported objective responses ranging from 4 to 33%. It is mainly due to differences in cycle doses, administered cumulative dose, as well as variabilities in patients' characteristics (such as various tumor types and patient performance statuses) that make these studies very difficult to compare. Different studies report median progression-free survival (PFS) varying from 17 to 29 months and median overall survival (OS) from 22 to 37 months [21–24].

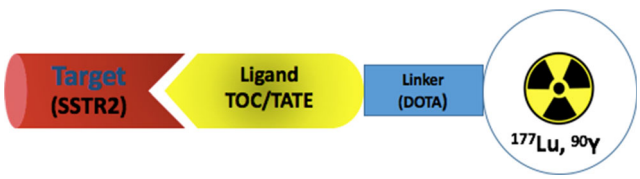

Fig. 2 An illustration showing the main components of PRRT: a radionuclide isotope like ^{90}Y, and ^{177}Lu, a ligand or carrier molecule like TATE or TOC, and a chelator or linker like DOTA that binds them together and stabilizes the complex

^{177}Lu-DOTATATE is currently the most widely used radiopeptide for PRRT [21]. It has shown similar efficacy when compared to ^{90}Y-DOTATOC, while showing a more favorable toxicity profile, especially when speaking of hematological and renal toxicity [25, 26]. In a recent study on bronchial and GEP-NETs, Brabander et al. [27] evaluated safety, efficacy and toxicity of ^{177}Lu-DOTATATE and showed impressive results. The objective response rate (ORR) reached 39%, stable disease (SD) was reported in 43% of patients, and the PFS and OS for all NET patients were 29 and 63 months, respectively (Fig. 3).

With time, the use of PRRT which initially targeted NETs was extended to other types of confirmed SSTR-positive tumors. Tumors such as breast cancer, lymphoma, glioma, meningioma, and paraganglioma, as well as non-iodine-absorbing differentiated thyroid cancer can now be considered for PRRT when registered therapies have failed [8].

^{177}Lu Radionuclide and NETTER-1 Trial

The Neuroendocrine Tumors Therapy (NETTER-1) trial is the first randomized controlled trial that evaluated the efficacy

Table 2 Characteristics of ^{111}In, ^{90}Y, and ^{177}Lu radionuclides [14]

Radionuclide	Maximum energy (MeV)	Penetration range (mm)	Further comments
^{111}In	0.61	0.5	Based on its physical features as well as gamma radiation, ^{111}In may be used for both imaging and treatment
^{90}Y	2.27	11	There is benefit in treating NETs with heterogeneous SSTR expression, but toxicity from targeting of adjacent healthy tissue remains a concern
^{177}Lu	0.49	2	Emission of gamma radiation can be used for dosimetry and monitoring of tumor response

and safety of ^{177}Lu-DOTATATE in patients with advanced, progressive, somatostatin receptor-positive midgut NETs [28]. This is the first phase III trial of its kind to reveal the significant impact of PRRT on the PFS and OS of patients with GEP-NETs compared to the standard conventional treatment.

The trial randomly assigned 229 patients who had well-differentiated, metastatic midgut NETs to receive either ^{177}Lu-DOTATATE with supportive octreotide LAR, or octreotide LAR alone. Compared to the 10.8% of the control group who were free of tumor progression at 20 months, 65.2% of those who received ^{177}Lu were free of tumor progression at 20 months. The response rate was 18% in the ^{177}Lu-DOTATATE group, significantly higher than 3% in the control group. The final analysis of overall survival has not been published yet, but a pre-specified interim analysis of overall survival was recently reported and has shown overall survival benefit. Hence, treatment with ^{177}Lu-DOTATATE resulted in markedly longer PFS and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Other studies on PRRT using ^{177}Lu-DOTATATE with their outcomes are summarized in Table 3.

New Approaches to PRRT Therapy

Combination of Radionuclides

Since every type of radionuclide has its own specific characteristics and effects, combining these radionuclides can be

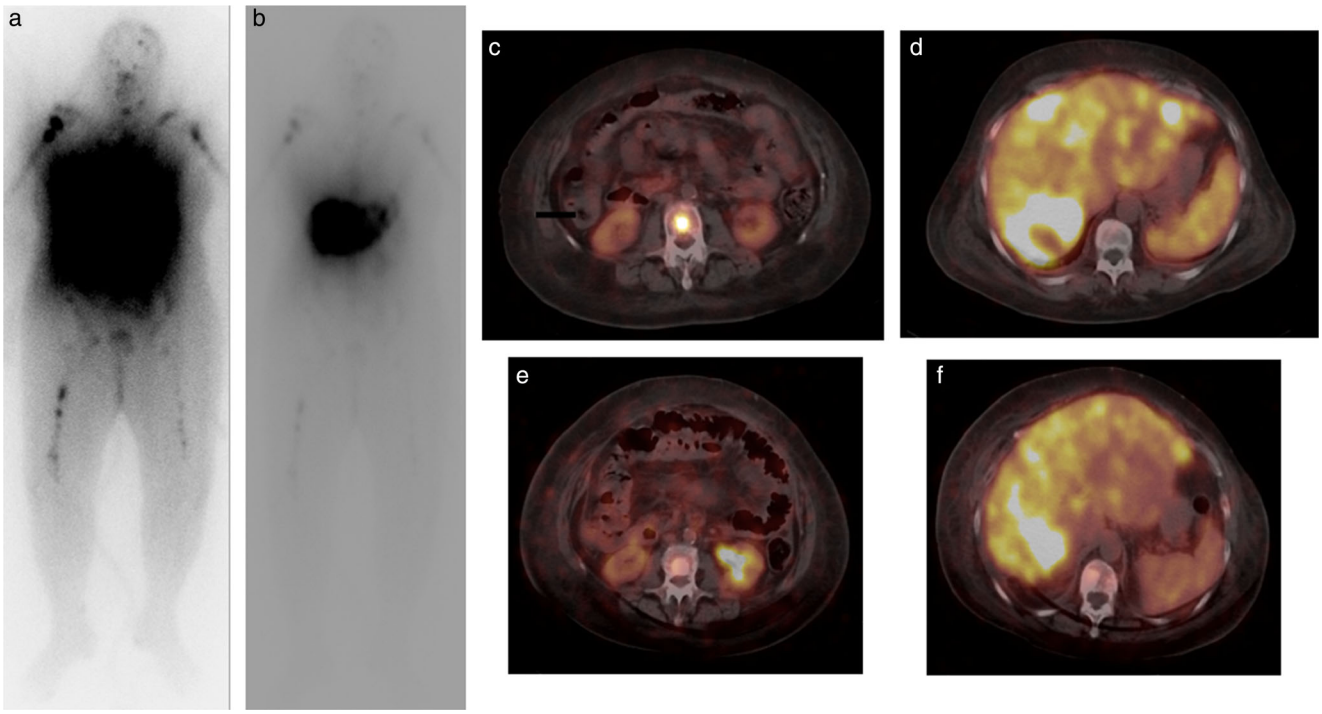

Fig. 3 **a** Anterior planar image of post-therapy scan after the first PRRT dose (^{177}Lu DOTATATE) shows extensive liver and bone metastases. (**b**) Anterior planar image of post-therapy scan for the patient after the third PRRT dose (^{177}Lu DOTATATE) shows a reduction in the intensity of radiotracer uptake in the liver and bone metastases, indicating partial response. Baseline axial ^{68}Ga DOTA-TOC PET/CT scans for the patient at the level of spine (**c**) and liver (**d**) show intense radiotracer uptake, reflecting the high expression of somatostatin receptors in the liver and bone metastases. Axial ^{68}Ga DOTA-TOC PET/CT scans at the level of the spine (**e**) and liver (**f**) after the third cycle of PRRT (^{177}Lu DOTATATE) show significant reduction in the radiotracer uptake, indicating partial response

Table 3 Summary of clinical studies on PRRT using ^{177}Lu-DOTATATE

Center (reference, year)	Patient number	Tumor response					
		CR, *n* (%)	PR, *n* (%)	MR, *n* (%)	SD, *n* (%)	PD, *n* (%)	CR + PR + MR + SD, *n* (%)
Rotterdam (Kwekkeboom et al [46], 2008)	310	5 (2)	86 (28)	51 (16)	107 (35)	61 (20)	240 (80)
Gothenburg (Swärd et al. [60], 2010)	26	0	6 (38)	N/A	8 (50)	2 (13)	14 (88)
Lund (Garkavij et al. [61], 2010)	12	0	2 (17)	3 (25)	5 (40)	2 (17)	10 (83)
Milan (Bodei et al [62], 2011)	42	1 (2)	12 (29)	9 (21)	11 (26)	9 (21)	33 (79)
Meldola (Sansovini et al [63], 2013)	26	3 (12)	7 (27)	N/A	12 (46)	4 (15)	22 (85)
Meldola (Paganelli et al [64], 2014)	25	1 (4)	0	N/A	20 (80)	4 (16)	21 (84)
Bonn (Ezziddin et al [65], 2014)	68	0	41 (60)	8 (12)	9 (13)	10 (15)	58 (85)
Bonn (Sabet et al [66], 2015)	61	0	8 (13)	19 (31)	29 (48)	5 (8)	56 (92)
Studies combining chemotherapy and PRRT							
Fremantle (Claringbold et al [34], 2011)	33	0	8 (24)	N/A	23 (70)	2 (6)	31 (94)
Fremantle (Claringbold et al [35], 2012)	35	5 (15)	12 (38)	N/A	13 (38)	3 (9)	31 (91)
Melbourne (Kong et al [67], 2014)	58	0	17 (30)	5 (9)	16 (29)	18 (32)	38 (66)
Melbourne (Kashyap et al [37], 2015)	40	1 (2)	11 (28)	N/A	27 (68)	1 (2)	39 (98)
New Delhi (Ballal et al [38], 2017)	88	0	30 (34)	8 (9)	44 (50)	6 (7)	82 (93)
Studies combining different radionuclides							
Warsaw (Kunikowska et al [30], 2011)	25	0	3 (12)	N/A	16 (64)	4 (16)	19 (76)
Basel (Villard et al [31], 2012)	134	3 (5)	28 (44)	N/A	32 (51)	0	63 (100)
Melbourne (Kong et al [68], 2017)	19	0	8 (42)	4 (21)	7 (37)	0	19 (100)

CR complete response, *PR* partial response, *MR* minor response, *SD* stable disease, *PD* progressive disease, *N/A* not applicable

used to achieve optimal therapeutic results. As mentioned before, ^{90}Y with its high electron-emitting energy (2.27 MeV) and high penetrability (up to 12 mm) is postulated to be more suitable for targeting larger-sized lesions, while ^{177}Lu with its relatively low energy (0.49 MeV) and penetration (2 mm) is considered a good candidate for targeting smaller lesions. This limitation is overcome by the longer biological half-life of ^{177}Lu. It has been suggested that combining these two radionuclides in patients with both small and large tumors, can achieve better results than using a single radionuclide alone. This was first shown in preclinical studies [29], and then a clinical trial held by Kunikowska et al. [30] supported this finding. The trial was conducted on patients with multiple metastatic lesions of different sizes. Of the 50 patients included in the trial, 25 patients were given ^{90}Y alone and 25 patients were given ^{177}Lu/^{90}Y combination. Longer overall survival was observed in the second group, and safety analyses in both groups were comparable. A study by Villard et al. [31] also replicated these findings, this time on a larger cohort of 486 patients divided into the same two groups.

Combination of Chemotherapy and Radionuclides

One of the promising approaches of Theranostics is the use of radiosensitizing chemotherapy in combination with PRRT to enhance treatment efficacy. Such a combination is useful for patients with aggressive metastatic NETs where a single agent is unlikely to yield any favorable results.

Ashwathanarayana et al. [32] reported the case of a young male patient of mediastinal paraganglioma with extensive skeletal metastases, who showed partial response and significant improvement in quality of life with combined ^{177}Lu-DOTATATE and low-dose capecitabine (5-FU oral prodrug). The patient eventually progressed 2 months after the 4th cycle.

After proving the safety of the combined therapy [33], trials were initiated to evaluate the efficacy of such treatment. Results of a nonrandomized phase II study [34] treating patients with a combination of capecitabine and ^{177}Lu-octreotate showed a 24% partial response (PR), 70% stable disease (SD), and 6% progressive disease (PD) in 33 patients. Three patients had to discontinue the drug due to treatment-induced angina, but were able to complete the intended 4 cycles of PRRT.

Claringbold et al. [35] treated patients with GEP-NETs with a combination of ^{177}Lu-octreotate, capecitabine, and temozolomide. Among 35 patients evaluated for tumor response, complete response (CR) was found in 15%, PR in 38%, SD in 38%, and PD in 9%. Median PFS was 31 months. The study showed that ^{177}Lu-octreotate in combination with capecitabine and temozolomide is well tolerated in patients with advanced low-grade NETs with significant tumor control rates. Another study by Claringbold et al. [36] was published later after 4 years of follow-up on patients with pNETs alone

receiving the same combination. Authors report a CR of 13% and PR of 70%, with no patients manifesting a PD, and the median PFS was 48 months. Both of these studies were uncontrolled and nonrandomized clinical trials. In a retrospective study, Kashyap et al. [37] showed favorable outcomes in patients with ^{18}F-FDG PET-positive GEP-NETs with advanced progressive ^{68}Ga-octreotate PET-avid disease with a combination of 5-FU and ^{177}Lu-octreotate. Among 52 patients, they report CR in 2%, PR 28%, SD 68%, and PD in only 2% of patients with median PFS 48 months.

A recent randomized clinical trial by Ballal et al. [38] established clinical efficacy of ^{177}Lu-DOTATATE combination with capecitabine over PRRT alone. According to RECIST 1.1 criteria, in the combination group, PR was achieved in 34%, SD in 50.2%, and PD in 6.8% of patients (compared to 6.3, 60.9, and 26.5% in the PRRT-only group, respectively), and the combination group was shown to have longer OS and PFS. No significant differences in hematological toxicity or hepatotoxicity were reported between both groups.

Neoadjuvant PRRT

The use of PRRT in patients with inoperable pNETs as neoadjuvant therapy, targeting tumor shrinkage, and making it more amenable to surgery is very promising. There are some case reports describing the use of neoadjuvant PRRT, particularly 90Y-DOTATATE in patients with pancreatic NETs who could be operated on successfully after PRRT [39–42].

Ezzidin et al. [43] reported a patient with pNET and liver metastases who received neoadjuvant therapy with ^{177}Lu-octreotate. There was a partial response with tumor shrinkage and a small residual metastatic liver lesion. The primary tumor was then completely resected and the patient remained in CR locally for 22 months postoperatively. Barber et al. [44] reported treating five patients with inoperable NETs with the combination of ^{177}Lu-octreotate and 5-FU. One of them underwent subsequent complete surgical resection and remained 12 months postoperatively alive and free of disease.

Van Vliet and colleagues [45] studied 29 patients with a pathology-proven nonfunctioning pNETs treated with ^{177}Lu-octreotate. After treatment, successful surgery was performed in nine patients (31%). The median PFS was 69 months for patients with successful surgery and 49 months for the other patients. Hence, neoadjuvant treatment with ^{177}Lu-octreotate is a valuable option for patients with initially unresectable pNETs.

Kwekkeboom et al. [46] retrospectively studied 310 patients with pNETs who received treatment with ^{177}Lu-octreotate. Four patients with partially responding nonfunctioning pNETs were able to undergo complete surgical resection. One of them died postoperatively from surgical complications. Recently, a study abstract from the European Pancreatic Club (EPC) 2017 meeting [47] compared patients with initially metastatic and/or locally advanced pNETs who underwent neoadjuvant PRRT with a group of patients who underwent upfront surgery. After PRRT, tumor size decreased from 59 to 50 mm, and the rate of curative resection was 65%. The 2-year progression-free survival rate was not significantly different between both groups (67% in neoadjuvant vs. 58% in control groups), but there was a lower risk of pancreatic fistula in the neoadjuvant group (25 vs. 65%) with comparable rates of complications (45 vs. 60%).

Adjuvant PRRT

PRRT may also be used in an adjuvant setting after surgery of GEP-NETs, preventing tumor growth after surgical manipulation or preventing further growth of pre-existing micrometastases. Unfortunately, only a handful of studies are available on postoperative treatment with PRRT. There are no published randomized trials on adjuvant PRRT favoring any evidence on the best treatment approach in this subset of patients.

One study [48] included patients with G1–G2 pNETs and synchronous liver metastases who were not eligible for liver surgery but were amenable to upfront PRRT. The prospective study followed 94 patients, 31 of whom previously underwent primary resection while the rest had no previous surgeries performed. Both groups were treated with PRRT, either ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE. The resection of the primary tumor was significantly associated with better PR or SD after PRRT and longer median PFS and OS for operated versus non-operated patients. In this study, only patients with synchronous pNET and liver metastases treated with PRRT were considered, excluding those who underwent primary tumor and liver surgery with radical intent. Patients affected by a G3 tumor according to the WHO 2010 classification and those who had undergone PRRT at disease progression under somatostatin analogs were excluded.

Even though it did not cover surgery per se, one study [49] compared patients who received PRRT who had received prior chemo or radionuclide hepatic embolization (CRHE) with those who did not have any prior history of such intervention. A total of 70% of patients who had CRHE (compared to 56.5% who did not) experienced benefit from ^{177}Lu PRRT, and 21.6% who had CRHE (compared to 35.8% who did not) experienced progression. Patients with a pervious history of CRHE also showed more SD and less PD following PRRT when compared to the patients who did not have any prior CRHE, but the probability of developing CR and PR is not statistically different between both groups.

To detect a difference in survival and/or tumor recurrence rate in patients treated with and without adjuvant PRRT, a large, multicenter trial with several years of follow-up would be needed.

Salvage Treatment

Although tumor response rates after initial treatment with PRRT are encouraging, CR is rare and eventually tumor progression occurs in the majority of patients. Retreatment with extra cycles of PRRT as salvage therapy may be considered when better options are not available. One study showed that salvage therapy with two additional cycles of ^{177}Lu-octreotate does not lead to serious hematologic or nephrotoxic side effects, but the tumor response rate was less compared with initial treatment [50].

Another report showed that long PFS after the initial treatment with PRRT predicts a prolonged PFS after salvage therapy [51], and argued that PRRT with ^{177}Lu-octreotate in the retreatment setting is a safe and effective option in patients with metastatic GEP-NETs. For these reasons, retreatment seems a good option for patients who responded well after the initial cycles of PRRT [52]. This novel and important concept of salvage therapy of NET needs to be tested in large, prospective, and multi-center trials to contribute to evidence-based findings.

Treatment Side Effects

PRRT is generally well-tolerated. Side effects can be divided to acute, subacute, and long-term side effects, as summarized in Table 4. Acute side effects are usually mild and self-limiting. Nausea or vomiting are related to the concomitant administration of kidney-protective amino acids. Subacute side effects are related to the radiopeptide itself, such as bone marrow suppression, mild hair loss (observed with ^{177}Lu-octreotate), or, more rarely, an exacerbation of a clinical syndrome. The most common subacute side effect of PRRT, occurring within 4 to 6 weeks after therapy, is bone marrow suppression. Usually, the hematologic toxicity is mild and reversible. More serious WHO grade 3 or 4 toxicity may occur, but this has been seen in less than 15% of patients [53].

Long-term side effects of PRRT may include renal failure as well as leukemia/myelodysplastic syndromes (MDS). Because radiopeptides are usually reabsorbed in the proximal tubules, they can accumulate in the renal interstitium and induce inflammation and fibrosis with eventual kidney damage. Co-administration of positively charged amino acids results in a reduction of renal radioactive uptake, up to 40% as reported in some studies [16, 54]. If patients have long-standing or poorly controlled comorbidities such as diabetes and hypertension that affect kidney function, it is expected that there would be a larger and more persistent decline in creatinine clearance [55].

Administration of Treatment

For purposes of kidney protection, positively charged amino acids, such as L-lysine and/or L-arginine, are co-infused to competitively inhibit the proximal tubular reabsorption of the radiopeptide [56]. This reduces the renal-absorbed dose. Dilution of the amino acids with saline allows proper hydration for the patient, an appropriate ratio to use is 25 g of amino acid in 1 L of normal saline. Obviously, patients' comorbidities should be taken into account (e.g., avoid volume overload in patients with cardiac insufficiency and take care in avoiding electrolyte imbalances with hyperosmotic solutions). Antiemetics can be administered before the infusion to avoid potential nausea or vomiting. Amino acid infusion should be started 30–60 min before administration of the radiopeptide and should be maintained over 4 h. Several amino acid protective schemes have been proposed in the joint IAEA, EANM, and SNMMI practical guidelines on PRRT treatment of NETs [56].

Current administration schedules comprise the most appropriate number of cycles (generally four or five) and the best delivery frequency (8 weeks apart). This pattern allows the patient to recover from the mild side effects of the therapy and increases its effectiveness in terms of the radiobiological activity [57]. Radioisotope infusion should be around 30 min as recommended in the literature. Vital signs (blood pressure and pulse as a minimum) should be monitored before and after therapy infusion in symptomatic patients. Therapeutic interventions should be performed to treat the functional syndrome effects or any exacerbations that may arise [56]. Treatment can be repeated to a limited extent, because of the limitations caused by bone marrow and kidney irradiation [12]. It was found that intra-arterial PRRT results in a greater uptake of radioactivity in liver metastases and tumor response rates seem higher than with intravenous administration. Long-term responses and toxicity data are not available yet [53].

Table 4 Acute, subacute, and long-term side effects associated with PRRT [53]

Acute	Subacute	Long term
Nausea, 25%	Bone marrow suppression	
Vomiting, 10%	Mild hair loss (more with ^{177}Lu) 60%	Renal failure
Abdominal pain, 10%	Exacerbation of clinical syndromes > 1%	Myelodysplastic syndrome
	WHO grade 3 or 4 toxicity < 15%	

Quality of Life

Patients' quality of life (QOL) is a vital aspect to look at after treatment with PRRT. Improvement is usually encountered after treatment with this modality. A study was run by Khan and his colleagues [58] and included 265 patients with inoperable metastatic GEP or bronchial NETs after ^{177}Lu-octreotate therapy. The study showed that symptoms improved significantly, regardless of the treatment outcome. One way to assess QOL of cancer patients is using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)-core module (C30). EORTC QLQ-C30 is a sensitive instrument for measuring changes in patients' performance status [59].

Conclusion

^{177}Lu PRRT is a new and promising treatment for patients with NETs, particularly those with grades 1 and 2, who are inoperable and have failed treatment with SSAs. In general, PRRT is well-tolerated and side effects are usually self-limiting in nature. It can be used as neoadjuvant treatment in patients with inoperable GEP-NETs, and as adjuvant therapy after surgical intervention. Combination treatments of PRRT with chemotherapy or targeted agents, as well as combinations of radionuclides in patients with NETs have been explored to some limits over the last few years. Retreatment with extra cycles of PRRT as salvage therapy has been evaluated in small retrospective series as well. Overall, there is evidence that disease control and quality of life improve significantly after ^{177}Lu PRRT therapy. The majority of patients with NETs experience partial responses or have disease stabilization; some 30% of patients, however, will have disease progression.

It is obvious from the literature review performed in this paper that there are a limited number of clinical trials conducted so far. This highlights the fact that there is still a need for large, prospective, multi-center, and controlled trials with several years of follow-up to contribute to current findings, and allow for the integration of PRRT in the treatment of NETs in clinical practice guidelines. NETTER-1 trial has provided a good level of evidence for the use of PRRT in GEP-NETs, and this approach should be duplicated in other potential indications for PRRT in NETs.

Compliance with Ethical Standards

Conflict of Interest Nader Hirmas, Raya Jadaan, and Akram Al-Ibraheem declare no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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