review articles

Neuroendocrine Tumors and Peptide Receptor Radionuclide Therapy: When Is the Right Time?

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abstract

Since its approval in 2018 by the US Food and Drug Administration, peptide receptor radionuclide therapy (PRRT) has become a mainstay in the treatment of neuroendocrine tumors. Lutetium-177-DOTATATE, the only approved agent, is indicated for the treatment of gastroenteropancreatic-neuroendocrine tumors. Although patient selection appears straightforward with somatostatin receptor-positron emission tomography, there is considerable complexity when deciding which patients to treat and when to start PRRT. Herein, we review the many factors that affect patient selection, focusing on the optimal patients to treat. Although significant effort has been expended to determine which patients benefit the most from PRRT, a validated predictive biomarker remains elusive. Although PRRT has been used for more than 2 decades in Europe and standards of care exist for safe treatment, there remain numerous questions regarding when PRRT should be used relative to other treatments. It is important to remember that multidisciplinary discussions are essential. Currently, there are a number of ongoing studies looking to assess the efficacy of PRRT compared with other treatment options and to optimize treatment through combination therapy, different dosing strategies, or use of different radionuclides and radioligands.

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KEY POINTS

- Lutetium-177-DOTATATE is approved for the treatment of somatostatin receptor–positive neuroendocrine tumors (NETs).
- Patient selection for peptide receptor radionuclide therapy is primarily based on somatostatin receptor-positron emission tomography.
- NETs vary on the basis of primary site, extent of disease, pace of growth, and other characteristics, and the appropriate sequence of therapies is complex and remains in flux.
- Multidisciplinary discussions are essential when choosing between therapeutic options for NET.

INTRODUCTION

Neuroendocrine neoplasms comprise a highly diverse spectrum of tumors that are classified on the basis of their primary site of origin and their pathology (differentiation and grading; Table 1). Neuroendocrine neoplasms are subclassified into well-differentiated (neuroendocrine tumors [NETs]) and poorly differentiated (neuroendocrine carcinomas) neoplasms, with well-differentiated tumors subclassified on the basis of their Ki-67 proliferation index and/or mitotic rate (MR) into grade 1 (G1) (Ki-67 between 1%-2%; MR < 2 per 10 high powered fields), grade 2 (G2) (Ki-67 between 3%-20%, MR between 2-20), and grade 3 (G3) (Ki-67 > 20%; MR > 20). In 2017 and 2018, the WHO classification was updated to include well-differentiated gastroenteropancreatic G3 tumors (WDG3), whereas previously, G3 NETs and neuroendocrine carcinomas were grouped together.[1,2] In patients with metastatic disease, the most common primary sites are the pancreas (Pan-NETs) and small

CONTEXT

Key Objective

How do we select patients optimally for peptide receptor radionuclide therapy?

Knowledge Generated

Neuroendocrine tumors vary on the basis of primary site, extent of disease, pace of growth, and other characteristics, and the appropriate sequence of therapies is complex and remains in flux. Systemic therapies include targeted agents such as everolimus and sunitinib, chemotherapies such as capecitabine/temozolomide, and somatostatin analogs. Debulking strategies include surgery and liver-directed therapies. A number of clinical trials are ongoing, focused both on how to improve upon peptide receptor radionuclide therapy and to better understand how to sequence therapies.

Relevance

Somatostatin receptor-positron emission tomography is currently used for patient selection, but a validated predictive biomarker remains elusive. Multidisciplinary discussions are essential when choosing between therapeutic options for neuroendocrine tumor.

bowel (SB-NETs), followed by the lung. Each of these tumors, depending on primary site and classification, has different behaviors and outcomes. In addition to their histological features and anatomic site, tumors can be functional, secreting a variety of bioactive compounds such as serotonin or peptide hormones (gastrin, insulin, vasoactive intestinal peptide, and others).

In patients with unresectable advanced disease, systemic treatment typically begins with somatostatin analogs (SSAs, octreotide, or lanreotide), which are also used for control of symptoms related to hypersecretion of serotonin or hormones. However, as outlined in a number of current treatment guidelines, the precise sequence of therapy must be individualized, on the basis of a variety of factors, including symptoms, comorbidities, prior therapy, tumor characteristics, and whether stability or shrinkage is acceptable.[3-5] In PanNETs, chemotherapy (either temozolomide- or streptozotocin-based) and targeted therapies including everolimus and sunitinib are often used.[6-9] In SB-NETs, SSAs and everolimus are approved, and everolimus is also approved for use in bronchial NETs.[10,11] Of note, the tyrosine kinase inhibitor surufatinib is approved in China for the treatment of advanced panNETs and extrapancreatic NETs, but has not been approved by the US Food and Drug Administration (FDA).[12,13]

Beyond systemic agents, given the predilection for the liver, liver-directed therapies (LDTs), such as bland embolization and chemoembolization, are commonly used. In selected patients, ablative therapies (radiofrequency or microwave ablation) are used.

The most recently approved therapy is peptide receptor radionuclide therapy (PRRT), which targets the somatostatin receptor (SSTR) using SSAs labeled with radioactivity. Yttrium-90 (90Y)–labeled compounds have been largely replaced by lutetium-177 (177Lu)–labeled compounds, in part because of the higher rates of renal toxicity with 90Y-labeled compounds.[14] In the only phase III trial (NETTER-1), 177Lu-DOTATATE (Lutathera) plus octreotide long-acting release (LAR) 30 mg once every 4 weeks was compared with high-dose octreotide LAR (60 mg once every 4 weeks) in patients with adequate renal function who had advanced SSTR-positive midgut NETs (Ki67 ≤ 20%) that were progressive despite standard dose octreotide LAR.[15] SSTR expression was defined using SSTR scintigraphy with 111In-pentetreotide (octreoscan). Treatment was shown to prolong progression-free survival (PFS) and improve patient quality of life.[15,16] The median PFS was 8.4 months (95% CI, 5.8 to 9.1) with octreotide LAR alone and was not reached in the PRRT arm (P < .001; hazard

TABLE 1. Heterogeneity Across Neuroendocrine Tumors

Primary Site	Lung	Midgut/Hindgut	Pancreas
Grade/differentiation	Low grade	Intermediate grade	High grade
		Well-differentiated	Poorly differentiated
Extent of disease		Low burden/resectable	High burden/unresectable
		Liver dominant	Widely metastatic
Pace of growth		Slow/stable	Progressive
Hormone status		Functional	Nonfunctional
SSTR expression		High expression	Low expression

Abbreviation: SSTR, somatostatin receptor.

ratio [HR] = 0.21; 95% CI, 0.13 to 0.33), although the overall response rate (ORR) with 177Lu-DOTATATE was only 13%.[15,17] There was also a trend toward increased overall survival (OS), although the difference was not statistically significant (P = .30).[18] 177Lu-DOTATATE was given in four cycles of a fixed 200 mCi administered activity intravenous over 30 minutes every 8 weeks; further details on administration can be found elsewhere.[19]

The NETTER-1 trial was performed in midgut NET (mostly SB-NETs), but the final FDA approval was for gastroenteropancreatic (GEP)-NETs and included Pan-NETs on the basis of prospective single-arm European data.[20] The authors reported a 55% ORR, median PFS of 30 months, and median OS of 71 months in Pan-NETs, although the ORR in the 177Lu-DOTATATE prescribing information for the same population was only 16% in GEP-NETs.[17,20]

National Comprehensive Cancer Network guidelines include PRRT as a potential therapy for SB-NETs, Pan-NETs, bronchial NETs, and paraganglioma/pheochromocytomas.[21] In SB-NETs, Society of Nuclear Medicine and Molecular Imaging/North American Neuroendocrine Tumor Society guidelines place PRRT before everolimus as a second-line therapy while European Society for Medical Oncology guidelines place PRRT before everolimus when the Ki-67 is < 10% and everolimus

before PRRT when the Ki-67 is > 10% and European Neuroendocrine Tumour Society guidelines place both everolimus and PRRT as second-line options.[3,22-24] In Pan-NETs, European Society for Medical Oncology and European Neuroendocrine Tumour Society guidelines place PRRT after capecitabine/temozolomide while Society of Nuclear Medicine and Molecular Imaging/North American Neuroendocrine Tumor Society guidelines placed both as second-line options. Overall, PRRT is recognized routinely in published guidelines, but treatment sequencing varies by society and primary site. Ongoing comparative trials (Table 2) will provide more evidence on sequencing of therapies as discussed below.

SELECTION OF PATIENTS FOR PRRT USING SSTR-POSITRON EMISSION TOMOGRAPHY

In NETs, SSTR imaging is used to select patients for PRRT. Historically, this was performed using SSTR scintigraphy with 111In-pentetreotide. Assessment of intensity of SSTR expression used the Krenning score,[25] a qualitative five-point score from 0 (Fig 1A, no uptake) to 4 (Figs 1C, uptake greater than the spleen). In NETTER-1, uptake greater than or equal to the liver (Krenning score of 2) was used as the inclusion criteria. It should be noted that 111In-pentetreotide has been mostly replaced with SSTR-positron emission tomography

TABLE 2. Selected Ongoing Phase II and Phase III Trials Involving Peptide Receptor Radionuclide Therapy in NETs

Trial	Sponsor	Tumor Type	NCT	Size	Comparison	Primary End Point	Estimated Completion
A021901	Alliance	Bronchial NET	NCT04665739	108	177Lu-DOTATATE 200 mCi × 4 v 10 mg everolims daily	PFS	2024
	NCI	Paraganglioma/pheochromocytomas	NCT03206060	90	177Lu-DOTATATE 200 mCi × 4 single arm	PFS	2026
NETTER-2	Novartis/AAA	G1/G2 GEP-NET	NCT03972488	222	177Lu-DOTATATE 200 mCi × 4 v high-dose octreotide	PFS	2027
LUTHREE	Romagnolo	Any SSTR-positive tumor	NCT03454763	618	177Lu-DOTATATE at every 5 weeks × 5 v every 8-10 weeks × 5	PFS and safety	2021
ReLUTH	Montpellier	All G1/G2 NET	NCT04954820	146	177Lu-DOTATATE 200 mCi × 2 v observation after two cycles of retreatment	RECIST response	2029
COMPOSE	ITM	G2/G3 GEP-NET	NCT04919226	202	177Lu-Edotreotide 200 mCi × 4 v CAPTEM/everolimus/FOLFOX	PFS	2026
COMPETE	ITM	G1/G2 GEP-NET	NCT03049189	300	177Lu-Edotreotide 200 mCi × 4 v 10 mg everolimus daily	PFS	2029
DOBATOC	Aarhus	All NEN	NCT04917484	100	177Lu-DOTATOC 200 mCi × 4 v modulated dosing × 4	PFS	2025
ALPHAMEDIX02	Radiomedix	G1-G3 NET	NCT05153772	34	212Pb-DOTAMTATE 67.6 μCi/kg × 4 single arm	RECIST response and safety	2023

Abbreviations: 177Lu, Lutetium-177; CAPTEM, capecitabine temozolomide; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; G1, Grade 1; G2, Grade 2; G3, Grade 3; GEP, gastroenteropancreatic; ITM, Isotope Technologies Munich; NCI, National Cancer Institute; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; PFS, progression-free survival; SSTR, somatostatin receptor.
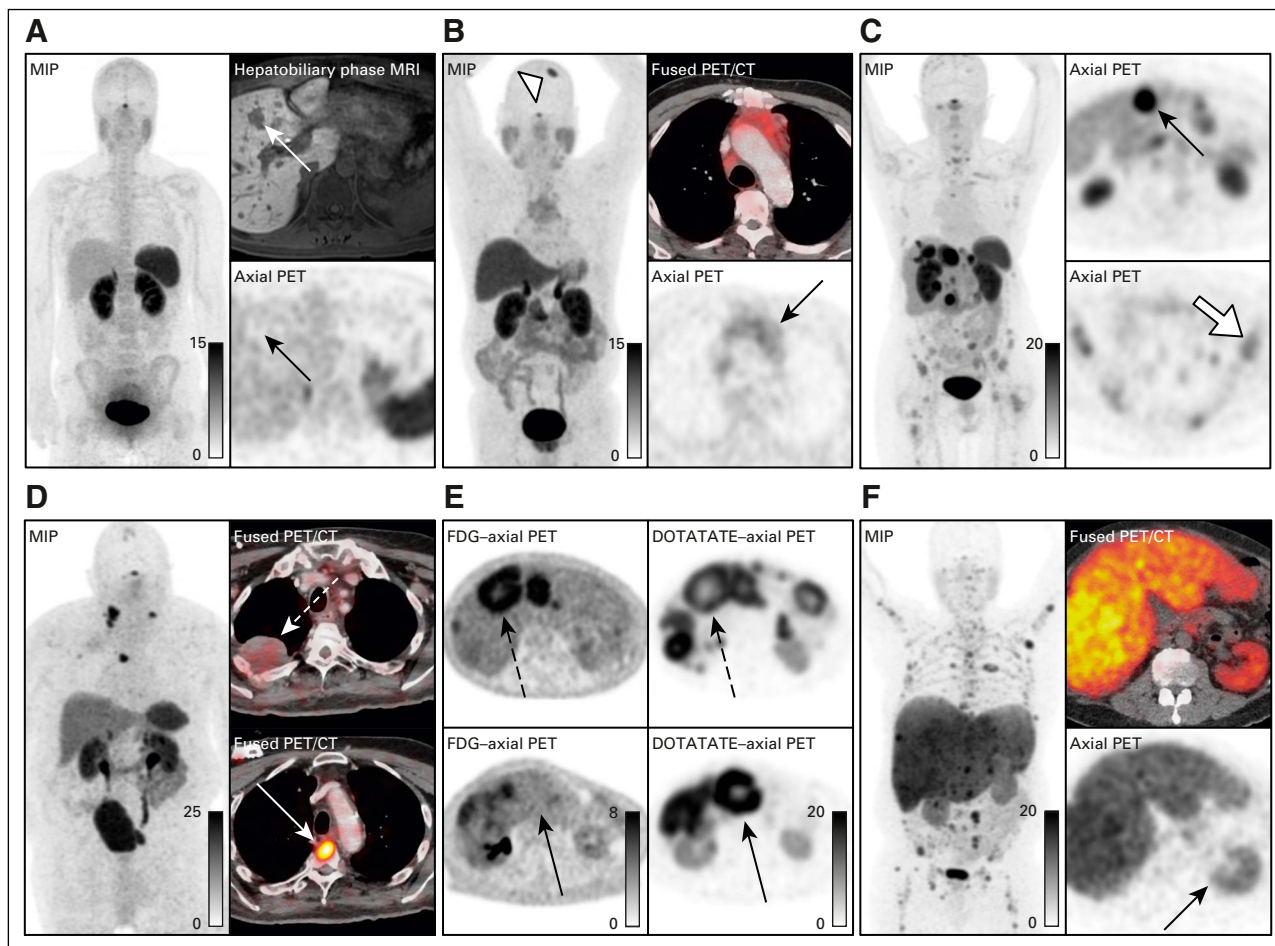
FIG 1. Issues with patient selection in SSTR-PET. (A) Patient A demonstrates no uptake in the liver lesions seen on hepatobiliary phase MRI (white arrow, Krenning 0) and is not a candidate for PRRT. (B) Patient B demonstrates uptake in the mediastinal mass above blood pool but less than the liver (black arrow, Krenning 1), which although technically has uptake, it is not adequate for treatment. There are benign causes of uptake on SSTR-PET, as seen in a meningioma in patient B (open arrowhead). (C) Patient C has uptake in some lesions greater than the liver and spleen (black arrow; SUVmax of 47, Krenning 4), but the bone lesions have uptake less than the liver (white arrow; SUVmax of 7.7, Krenning 2). Given that the bone lesions were the site of progression, PRRT is not a good option. (D) Patient D has lesions with high uptake in the thoracic spine (dotted white arrow) while other sites of disease, for example the pulmonary nodule, have no uptake on SSTR-PET (solid white arrow). Therefore, the patient is not a candidate for PRRT. (E) Patient E has disease that is heterogeneous when comparing FDG with SSTR-PET. Some lesions have uptake on both FDG and SSTR (dotted arrows) while other lesions are positive on SSTR and negative on FDG (solid arrows). In this case, the patient maybe a candidate for PRRT. (F) Patient F has uptake greater than the liver and spleen (SUVmax of 12), although all uptakes are diminished because of the large volume of tumor and kidney uptake is relatively decreased (black arrow). This patient meets criteria for treatment but has a poor prognosis because of the large tumor volume. CT, computed tomography; FDG, fluorodeoxyglucose; MIP, maximum intensity projection; MRI, magnetic resonance imaging; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SSTR, somatostatin receptor; SUVmax, maximum standardized uptake value.

(PET) using one of the three FDA-approved agents (68Ga-DOTATATE, 68Ga-DOTATOC, and 64Cu-DOTATATE). SSTR-PET is a marked improvement over 111In-pentetreotide in regards to lesion detection.[26] Although there are slight differences in the three SSTR-PET radiopharmaceuticals, they are treated as equivalent for patient selection for PRRT. Krenning scores applied to SSTR-PET (often termed as modified Krenning scores) are not equivalent to 111In-pentetreotide, and SSTR-PET typically results in higher scores particularly in patients with smaller lesions.[25,27] Of note, disease can technically have uptake on SSTR-PET, but not have high enough uptake for PRRT (Fig 1B).

Uptake on PET can be quantitatively measured using the standardized uptake value (SUV), which corrects measured activity in an individual volume for the mass of the patient. SUVs are typically reported as the maximum SUV, which is the voxel with the highest measured uptake in the lesion of interest. Unfortunately, SUVs are affected by more than just receptor density, for example high-volume tumor can serve as sink for the radioligand decreasing measured uptake across tissues (Fig 1D). Another important issue with SSTR-PET is the presence of heterogeneous disease. Within patients, there can be disease that is both SSTR-

positive (Krenning 3 and 4) and SSTR-negative (Krenning 0-2; Fig 1C).

SSTR-PET AS A PREDICTOR OF RESPONSE

There has been a number of efforts to predict response to PRRT using baseline SSTR-PET images, but before going further, it is important to review the difference between prognostic and predictive biomarkers.[28] A prognostic biomarker will identify the likelihood that a patient will have a more or less favorable outcome, regardless of therapy. An example of a prognostic biomarker is tumor growth rate (TGR), and as expected, a higher TGR correlates with progression.[29] A predictive biomarker will separate similar individuals into those that are more or less likely to respond to a specific intervention or experience a certain toxicity. SSTR-PET is both a predictive and prognostic biomarker, but it should be noted that developing predictive biomarkers typically requires evaluation in a population of patients (with and without the biomarker) treated with two different therapies. A predictive marker must also predict response reliably enough to affect treatment choices. One confounding factor with SSTR-PET is that uptake is related to proliferative rate and differentiation, with more aggressive tumors having lower uptake.[30] For example, in patients treated with SSAs, higher SUVs correlate with longer PFS,[31] but whether or not this is due to SSAs being more effective in patients with higher SSTR-PET uptake or because of patients who are likely to have better outcomes is not clear.

A number of studies have correlated higher pretreatment SSTR-PET uptake to better PRRT outcomes.[32,33] The only randomized trial with PRRT (NETTER-1) used 111In-pentetreotide for baseline imaging.[15] There was no difference in the HR of patients who were Krenning 4 versus those with lower uptake (HR = 0.23 v 0.18), suggesting that we should be careful when using SUVs to select which patients to treat with PRRT and that further work needs to be performed to determine how SSTR-PET should be used as a predictive biomarker.[15] In spite of this, there appears to be benefit to having higher uptake on SSTR-PET before PRRT as pretreatment uptake correlates with subsequent measured dose to the tumor,[34] and the mechanism of action is dependent on dose delivery with higher doses having more response.[35] Therefore, although there are no absolute cutoffs on which to make clinical decisions, when faced with multiple treatment options, higher uptake on SSTR-PET may sway one toward PRRT.

In addition to uptake on SSTR-PET, heterogeneity may be equally as important for patient selection. Patients with heterogeneous disease on SSTR-PET have worse outcomes, including OS.[36,37] SSTR-negative lesions will not respond and are associated with primary treatment resistance because of the absence of the target.[38]

An alternative to pretreatment cutoffs is to use post-treatment imaging to evaluate response during therapy. In addition to emitting an electron, 177Lu emits gamma photons that can be imaged using a single-photon emission computed tomography camera. Using quantitative techniques, one can calculate absorbed dose in organs and lesions, which may become more feasible with newly described single time point imaging techniques.[39,40] Ultimately, radiographic response takes into account both intrinsic radiation sensitivity and dose to the tumor and can allow an evaluation of treatment efficacy during treatment. Figure 2 shows a patient with relatively low uptake on SSTR-PET (maximum SUV of 13.6), who demonstrated an impressive response after only one cycle of 177Lu-DOTATATE.

DEVELOPING ROLE OF CIRCULATING BIOMARKERS

Nonhormonal tumor markers, particularly chromogranin A, are frequently used,[41] but rarely affect patient management.[42] Although chromogranin A at baseline was shown to be prognostic for PFS and OS in multiple studies including the RADIANT trials,[10,43] it has not shown to be predictive of response to PRRT or other treatments most likely because of its high false-positive and false-negative rates.[44] Taken together, there is no clear role for chromogranin A as a biomarker for patient selection for PRRT.

The primary issue of using either SSTR-PET or nonhormonal tumor markers to predict response to SSTR-PET is that they do not take into account tumor-specific factors, primarily the radiosensitivity of the tumor. Circulating biomarkers can potentially measure the intrinsic sensitivity of a tumor, which could be used as a predictive biomarker for PRRT. Blood-based genomic markers include the NETest and the PRRT Predictive Quotient (PPQ). The NETest, a 51 gene assay of circulating transcripts, is under study as a biomarker of PRRT response.[45] The NETest has shown prognostic value in for predicting outcomes after curative surgery or systemic therapies including PRRT. PPQ combines eight blood gene transcripts with the Ki-67 of the tumor to create a binary output of response to PRRT.[46] Two studies assessing the PPQ in non-PRRT cohorts suggest that it might be a predictive biomarker[46,47]; however, data from randomized trials are not available. Although not evaluated in the setting of PRRT to date, the presence and increased fractions of circulating tumor DNA were associated with poorer PFS.[48] Further work using circulating tumor cells and DNA may add additional value in understanding who will benefit the most from PRRT.

LOW-VOLUME DISEASE

The decision of when to start systemic therapy and particularly 177Lu-DOTATATE is not clear. In patients with low-volume disease, especially slow-growing disease, systemic therapy is often best postponed or a treatment with low toxicity such as SSA may be considered.[11,49] Overall, NET patients with low-volume disease do better than patients with higher-volume disease; for example, in the PROMID trial
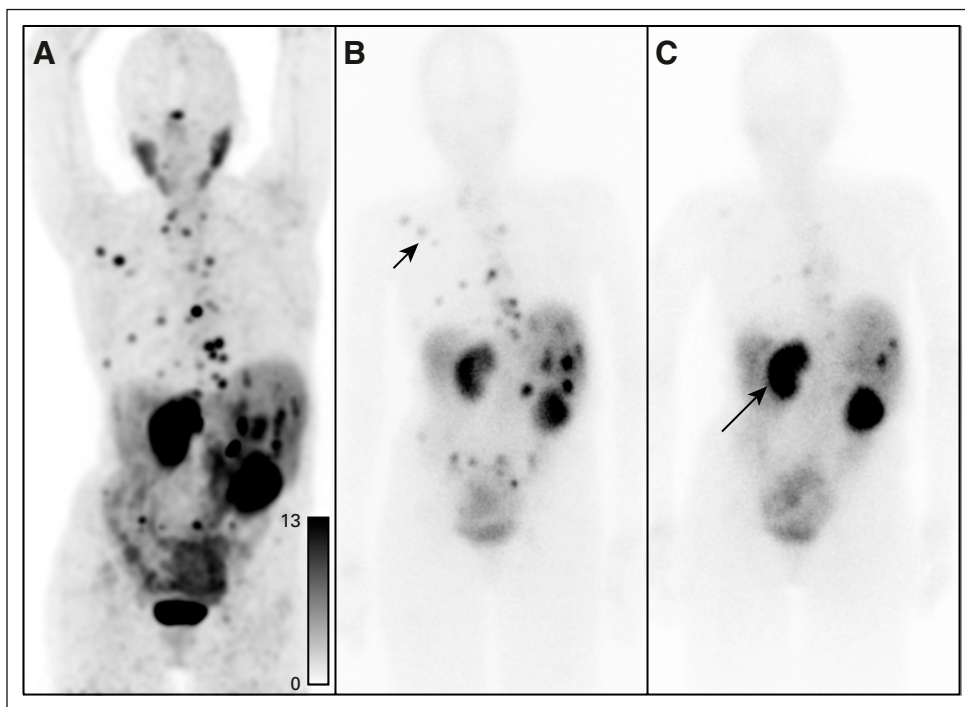
FIG 2. Post-treatment imaging for evaluation of response. A 70-year-old woman with pancreatic neuroendocrine tumor treated with two cycles of 177Lu-DOTATATE. (A) Pretreatment 68Ga-DOTATATE PET demonstrates SSTR-positive disease, with standardized uptake values up to 13.6. (B) Postcycle 1 planar gamma camera imaging demonstrates uptake in the osseous and hepatic disease (black arrowhead). (C) Postcycle 2 planar gamma camera imaging demonstrates increased uptake in the kidneys (black arrow) and significant reduction in uptake in the previously visualized disease consistent with response. PET, positron emission tomography; SSTR, somatostatin receptor.

of octreotide versus placebo in midgut NET, the median time to progression on the treatment arm decreased from 29.4 months in patients with 0%-10% liver involvement to 4.6 months in patients with > 50% liver involvement.[49] Similarly, indolent disease course was demonstrated in the CLARINET trial, a placebo controlled trial of lanreotide in GEP-NET.[11]

One issue with this approach is defining low-volume disease. In PROMID, low-volume disease was considered as patients with < 10% liver involvement, whereas in CLARINET, it was 25% liver involvement.[11,49] Another limitation is that the assessment of tumor volume from published trials is restricted to the liver and does not consider disease spread to other sites such as the bone, lung, or peritoneum. Given the difference in detection rate between 111In-pentetreotide and SSTR-PET, one might consider lesion sizes < 2 cm as low-volume disease.[27] In addition to volume, tumor grade is important. In the CLARINET study, the median PFS for placebo decreased from 18.3 months in G1 tumors to 12.1 months in G2 tumors.[11]

If time to progression on octreotide is as long as 29 months in low-grade midgut NET with low-volume disease, might it be appropriate to postpone the onset of systemic therapy? Given that PRRT can have significant long-term toxicities,

primarily bone marrow and renal, delaying treatment is appealing. In GEP-NET patients with low-volume disease and a slow pace of growth, alternative strategies might include local therapies, higher-dose SSA, or even an oral agent (eg, everolimus or sunitinib) although potential toxicity should be factored in. Although not routine, emerging data suggest that treatment with SSAs may be appropriate beyond progression with dose intensification.[15,50] In short, low-volume disease presents a unique challenge given a lack of data to guide therapy decisions and the potential for toxicities in patients who might otherwise have a relatively good prognosis.

HIGH-VOLUME DISEASE

The higher the volume of disease, the worse the outcome.[51] Many prognostic factors including > 50% liver involvement, more than five bone metastases, or a highly elevated chromogranin A all correlate with poor outcomes after PRRT.[52] In patients with high-volume disease treated with 177Lu-DOTATATE, tumor sink results in decreased uptake and, therefore, lower efficacy.[53] In a secondary analysis from the NETTER-1 trial, higher tumor volume was associated with poorer outcomes, but only the presence of liver lesions > 3 cm was predictive of a worse outcome.[54]

Therefore, it may be optimal to debulk patients before PRRT, which could be performed with surgery, LDT, or chemotherapy. LDT is effective in debulking larger hepatic lesions, and the RETNET trial (ClinicalTrials.gov identifier: NCT02724540) will help us understand which type of embolic therapy is optimal. In particular, radioembolization should be reserved for patients with SSTR-negative tumors or those who have localized large SSTR-positive tumors, where selective arterial administration can be used to spare normal liver.[55] In patients with high-volume Pan-NET, treatment with capecitabine/temozolomide can be used given the 33% ORR observed in the E2211 study, which showed a median PFS for temozolomide of 14.4 months versus 22.7 months with capecitabine/temozolomide (HR = 0.58, P = .023).[7] Two important studies, A022001 (177Lu-DOTATATE versus capecitabine/temozolomide in Pan-NETs) and COMPOSE (177Lu-Edotreotide versus best standard of care in GEP-NETs; Table 2) will help to address the question of sequence chemotherapy and PRRT.[56]

One important consideration with LDT is that relatively fast debulking can be beneficial in symptomatic patients or those who have a high urine 5-HIAA or hypersecretion of peptide hormones. However, PRRT can also be effective in hormonal symptom control as well, with one series showing 71% of functional Pan-NET patients with uncontrolled symptoms at baseline had improvement.[57] In SB-NET, symptomatic improvement is often seen without a radiographic response. For example, with Y90-DOTATOC, only 4% of patients had a radiographic response while 42% had improvement in diarrhea,[14] and in the NETTER-1 study, only 13% had a radiographic response while 48% had improvement in diarrhea.[16]

COMPLIMENTARY ROLES OF SSTR AND FLUORODEOXYGLUCOSE-PET IN HIGHER-GRADE NETs

The majority of evidence for PRRT is in G1/G2 NETs, although PRRT is beneficial in patients with G3 NETs.[58-60] The largest retrospective multicenter study evaluated 149 patients with G3 NETs and demonstrated a 42% ORR, 14-month PFS, and 29-month OS.[59] The higher the Ki-67, the worse the outcome with PFS falling from 16 months to 6 months when the Ki-67 was > 55%. Compared with G1/G2 NETs, WDG3 NETs have a higher ORR, but shorter PFS.

Imaging is important when selecting higher-grade NETs for PRRT. 18F-fluorodeoxyglucose (FDG) is a marker of tumor metabolism and uptake increases with more aggressive tumors. Converse to SSTR-PET, higher uptake on FDG-PET correlates with worse outcomes and has been shown to outperform pathologic grading.[61] Although often FDG and SSTR-PET uptake are inversely correlated, they can be unrelated and, therefore, the NETPET score was developed to take into account differing uptakes.[62] In general, patients with higher uptake on FDG-PET have a higher score, have a poorer outcome, and are less suitable candidates for PRRT.[63] As discussed above, heterogeneous SSTR expression is a poor prognostic factor, and the combination of FDG and SSTR-PET can help to further elucidate variation across metastases. It is important to make sure that there are not lesions that are FDG-positive and SSTR-PET–negative as these sites of disease will not be successfully treated with PRRT. Although less commonly used in the United States, FDG-PET is recommended by the European Association of Nuclear Medicine not only in G3 cases but also in patients with rapidly progressive disease and those with SSTR-negative disease on computed tomography.[64]

As FDG-PET is a marker of metabolism, uptake likely relates to both TGR and proliferation rate, and both higher FDG uptake and TGR are poor prognostic factors.[29,61] As a simplification of radiation sensitivity and a modern application of the law of Bergonié and Tribondeau, it is often considered that tumors with higher TGR, Ki-67, and uptake on FDG (all markers of higher proliferation rates) are more sensitive to radiation.[65] Although this may be true, patients with WDG3 tumors who have higher Ki-67 and higher uptake on FDG-PET have lower ORR, PFS, and OS after treatment with PRRT.[60] Although PRRT is approved in patients with progressive disease, patients without documented tumor progression who have high-volume disease or higher-grade disease may be considered for treatment, as is being evaluated in COMPOSE and NETTER-2 (ClinicalTrials.gov identifiers: NCT03972488 and NCT04919226).

LIMITATIONS AND CHALLENGES

There are many challenges for patient selection. Pre-existing liver, renal, and bone marrow dysfunction can be worsened with treatment. In patients with liver injury, it is difficult to decide if PRRT is safe. One study showed a high rate of toxicity in heavily pretreated liver-dominant patients after receiving PRRT with nearly 60% of patients developing ascites[66] while other studies have shown that regional hepatic embolization is safe before PRRT.[67] Although there are no data on the use of PRRT after Y90-radioembolization, it appears that Y90-radioembolization is safe after PRRT.[68,69] Limited LDT before PRRT is safe, yet PRRT may worsen liver injury in patients with ascites or other signs of liver failure.

Renal injury has been demonstrated with Y90-based treatments,[70] but it appears that the rate of renal toxicity is lower with 177Lu-labeled compounds, and it is not clear what the rate of renal injury is with 177Lu-DOTATATE. The NETTER-1 trial did not demonstrate any toxicity related to PRRT in patients with mild renal dysfunction.[71] Renal toxicity is likely more an issue in the setting of repeat PRRT because of the cumulative kidney dose, although in one study of 168 patients receiving repeat PRRT, there were no cases of grade III or IV renal toxicity.[72] One difficulty with renal toxicity is that it develops months to years after treatment, and, therefore, one cannot dynamically evaluate for toxicity during the 6-month course of therapy. The delay in development of renal toxicity also limits the reports of renal injury in the literature. Although renal injury appears

uncommon with PRRT, as repeat treatments become more common, we will have to address cumulative injury to the kidneys.

Bone marrow toxicity is typically acute, and evaluating for cytopenias between cycles is straightforward. In contrast, long-term bone marrow toxicity (leukemia and myelodysplasia) occurs in 2%-3% of patients typically 1-4 years after treatment.[18,20,70] There are no predictive biomarkers, and myeloid neoplasms are typically predated by the development of thrombocytopenia.[73] The risk appears to be higher when concurrent chemotherapy is administered, limiting the value of this approach.[74,75] Early work suggests that clonal hematopoiesis may relate to the development of cytopenias and potentially secondary myeloid neoplasms.[73,76] In patients with advanced NET, the median survival is measured in years, with a subset of patients living decades, and, therefore, the risk of secondary bone marrow malignancies can be the biggest concern.

Additionally, how to treat patients with mesenteric and peritoneal disease, who may develop subsequent bowel obstructions, has yet to be determined.[77,78] It is generally agreed upon that steroids should be used in patients with mesenteric or peritoneal disease to prevent complications. Importantly, PRRT is not effective in decreasing the size of mesenteric masses in SB-NETs and is likely not beneficial in treating bowel complications.[79]

One last issue relates to patients with poor performance status (PS). Anecdotally, patients can have poor outcomes from PRRT if they have a poor baseline PS, and poor PS has been shown to be an independent prognostic factor for OS

after PRRT.[80] However, precise information is lacking as such patients are not candidates for clinical trials.

OPTIMIZING PRRT

The current implementation of PRRT is to administer a unit dose of 200 mCi per cycle for a total of four cycles. There is over a 10-fold variation tumor absorbed dose with PRRT because of the widely different extents of disease and varying tumor uptake.[81] A patient-specific dosing protocol would be optimal, but consensus on how this should be performed remains elusive. A handful of trials (Table 2) are being performed by modulating the administered activity on the basis of measured kidney absorbed dose,[82,83] but none to date are targeting an optimal tumor absorbed dose. Significant work needs to be performed to determine the optimal number of cycles, frequency of cycles, and administered activity moving forward.

In liver-dominant patients, a method to increase the efficacy of PRRT is to administer the activity intra-arterially rather than intravenously. Initial work using 68Ga-DOTATOC demonstrated an over three-fold increase in tumor uptake in hepatic lesions when administered intra-arterially,[84] although a subsequent study with 90Y-DOTATOC did not reproduce such impressive results.[85] There are currently multiple trials looking at the benefit of intra-arterial administration (ClinicalTrials.gov identifiers: NCT03590119 and NCT03590119).

One other approach to improving the efficacy of PRRT is to use combination therapy approaches. One of the first approaches was to combine PRRT with chemotherapy such as capecitabine/temozolomide (ClinicalTrials.gov
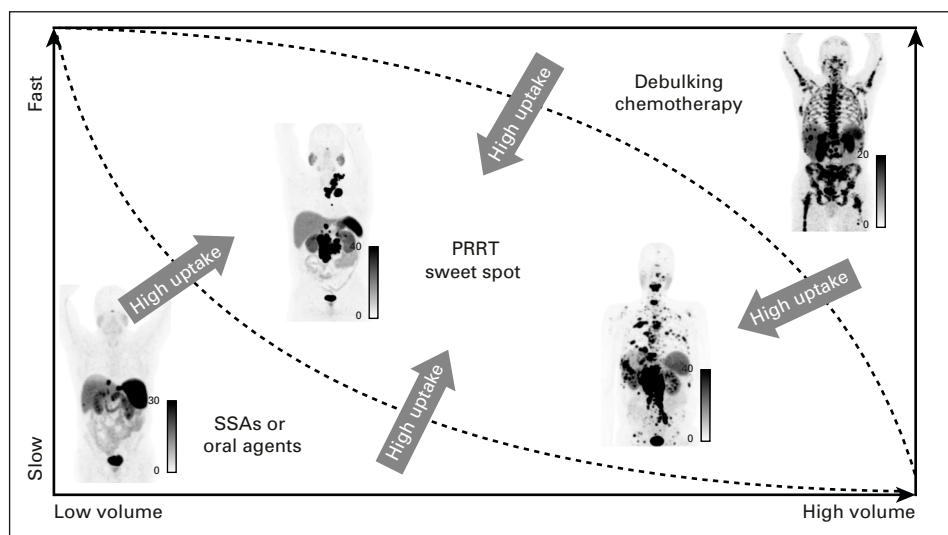

FIG 3. Optimal setting for PRRT. Patients with low-volume disease that is relatively stable may be better treated with SSAs, oral-targeted agents, or even observation. Patients with high-volume disease may benefit from debulking therapies before PRRT or chemotherapy. If disease is faster pace or higher-grade, PRRT may be appropriate in lower-volume patients. Additionally, the higher the uptake on somatostatin receptor-positron emission tomography, the better an option PRRT becomes relative to other therapies. Overall, patient selection remains complex, and multidisciplinary tumor board discussions are needed to determine optimal treatment strategies. PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog.

identifier: NCT02358356), although early reports from a prospective RCT and long-term follow-up data from a phase II study indicate that the rate of marrow toxicity, including myelodysplastic syndrome and acute leukemia, is unacceptably high.[74,75] Other trials are studying the combination of therapies that impair DNA repair such as olaparib (ClinicalTrials.gov identifiers: NCT04375267 and NCT04086485) and triapine (ClinicalTrials.gov identifier: NCT04234568), although there may be similar concerns with marrow toxicity.[86] Finally, although single-agent check point inhibitors have not been successful in NETs,[87,88] combinations with PRRT are being evaluated (ClinicalTrials.gov identifier: NCT03457948); preclinical data showing antitumor immune responses by PRRT with 177Lu-DOTATATE in a murine model of human NET support this strategy.[89]

FUTURE DIRECTIONS

There are currently a number of phase II/III trials in NETs (Table 2), primarily focused on new indications (eg, bronchial NET and paraganglioma/pheochromocytomas), radioligands (DOTATOC and Edotreotide), radionuclides (212Pb), retreatment, modulated dosing, and assessing treatment earlier in the disease course. With the approval of 177Lu-DOTATATE, the field continues to move quickly to adapt to the introduction of this new treatment modality.

In March 2021, the National Cancer Institute Gastrointestinal Steering Committee convened a clinical trials planning meeting focused on NETs.[56] There were two immediate term concepts that were discussed: the role of retreatment with PRRT and modified PRRT on the basis of lesional absorbed dose. Additionally, combination trials with immunotherapy and DNA repair–targeted therapies were considered. Although not discussed at the NET clinical trials planning meeting because of feasibility concerns, there is a considerable interest in the use of alpha particle therapy in NETs. Alpha particles (a helium atom) are much larger than beta particles (an electron) and so deposit their energy over a much shorter distance (50-60 m v 1-2 mm). A single-center phase I study evaluating 212Pd-DOTAMTATE demonstrated an 80% ORR in patients treated at the recommended phase II dose.[90] Early work has also shown efficacy with 225Ac-DOTATATE and 225Ac-DOTATOC but has been limited to single-center series to date.[91,92]

NETs are a heterogeneous disease with many unanswered questions. Although the selection of patients for PRRT is based on uptake on an imaging biomarker, we lack a predictive biomarker to help select which patients are most likely to benefit from PRRT. Overall, there is likely a sweet spot for PRRT where patients with low-volume disease are followed with observation or treated with SSAs, whereas high-volume patients or those with a fast TGR may be best treated with chemotherapy or other debulking approaches (Fig 3). Everything being equal, higher uptake on SSTR-PET would make one consider PRRT over other options, although no strict cutoffs exist. This is similar in concept to that proposed by Hofman and Hicks[93] previously, which focused on the integration of information from functional imaging, SSTR, and FDG-PET on one side and proliferative activity on the other. We acknowledge that this approach is overly simplified and urge the use of multidisciplinary discussions to evaluate treatment options for individual patients, in order integrate key factors such as functionality, TGR, prior therapies, patients features, and comorbidities. We are fortunate that the field is rapidly moving forward, and many opportunities to optimize and improve upon PRRT are being evaluated.

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