Peptide Receptor Radionuclide Therapy for Advanced Neuroendocrine Tumors

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KEYWORDS

• Bone marrow • Bronchopulmonary • Carcinoid • Gastroenteropancreatic neuroendocrine tumor • Hepatic neuroendocrine metastasis • Peptide receptor radionuclide therapy • PRRT • Renal toxicity

KEY POINTS

- Peptide receptor radionuclide therapy (PRRT) with either ^{90}Y-octreotide or ^{177}Lu-octreotate is an efficient and relatively safe treatment of unresectable or metastatic neuroendocrine tumors.
- Over 2 decades, PRRT has been demonstrated to provide effective tumor response, symptom relief, and quality-of-life improvement, biomarker reduction, and, ultimately, a positive impact on survival.
- PRRT is generally well tolerated. Chronic and permanent effects on target organs, particularly the kidneys and the bone marrow, are generally mild if appropriate precautions are undertaken.

INTRODUCTION

Neuroendocrine neoplasms are variously referred to as "carcinoids," neuroendocrine tumors (NETs), or gastroenteropancreatic (GEP) neuroendocrine (NE) neoplasms (GEP-NENs).[1] Most NETs are located in the gastroenteropancreatic tract and in the lung (**Fig. 1**).[1] In general, they are slow-growing tumors but in some instances may behave in a highly aggressive fashion (neuroendocrine carcinoma; NEC).[2] Due to their diverse and protean symptoms (sweating, flushing, diarrhea, bronchospasm, and anxiety), diagnosis is often significantly delayed and lesions therefore are only identified when metastatic spread has occurred. Metastasis can occur locally, in the mesentery, in adjacent lymph nodes, and by hematogenous spread. In most, the liver is the dominant site of metastatic spread, but lung, bone, and brain may also be affected.[3] As a consequence of the substantial percentage of individuals with metastatic disease, most therapeutic strategies are directed at the management of hepatic secondaries or local recurrence.[4]

Given the different organ distribution of the primaries and their widely different biologic behavior,

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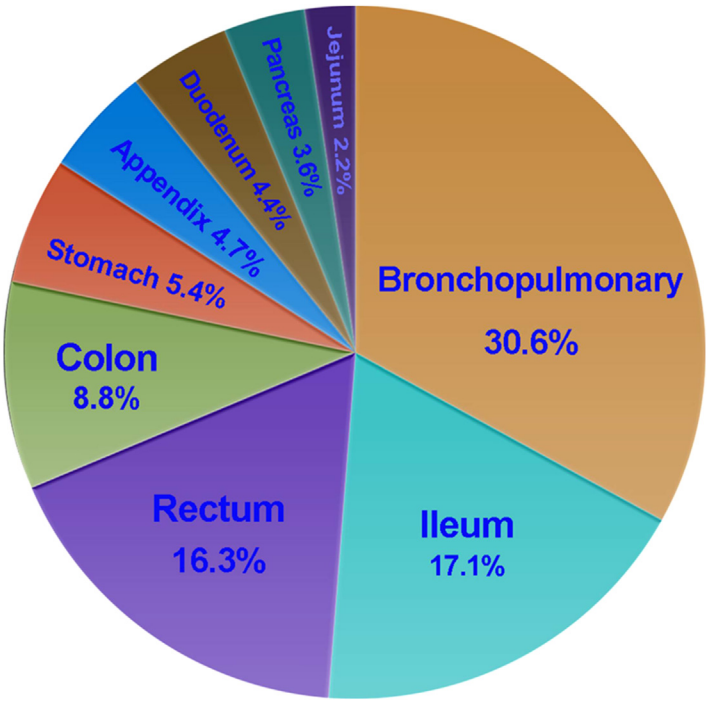

Fig. 1. Incidence of different types of NETs. Most are located in the gastroenteropancreatic tract and the lung.

treatment of NETs is typically multidisciplinary and is individualized according to the tumor type, extent of the disease, and level of symptoms. GEP-NENs were previously considered rare, but in fact, not only are increasing in incidence (3.65/100,000), but also occur as frequently as testicular tumors, Hodgkin disease, gliomas, and multiple myeloma.[1] They represent a significant clinical issue for 2 reasons. First, at diagnosis, 40% to 95% are metastatic (depending on the primary site) and, second, there is a paucity of evidence-based best practice strategies.[1] A key management issue is that at diagnosis, 65% to 95% of GEP-NENs (excluding appendiceal and gastric NETs) have metastasized to the liver.[5,6] Therapeutic endeavors are therefore in most instances focused on the management of metastatic disease, and neuroendocrine liver metastases (NE LMs) represent one of the most significant prognostic factors irrespective of the primary tumor site. Thus, the 5-year survival in historical series is 13% to 54% compared with 75% to 99% in individuals without hepatic metastases.[7,8]

Recent experience from some specialized centers documents improved 5-year overall survival rates of 56% to 83% for metastasized intestinal NENs and 40% to 60% for pancreatic NENs.[9] Although these data have been used to suggest that NET management should only be undertaken at specialized centers, such proposals may not be realistic in the current medical economic climate. Despite the use of a diverse variety of complex management strategies for NE LMs, surgery remains the only treatment option with the potential to cure.[9] For unresectable tumors, optimal selection of palliative treatment options (timing and modality) is of paramount importance to maintain or improve quality of life (QoL) and prolong overall survival.

OVERVIEW

Unlike many well-studied neoplastic diseases such as breast or colon cancer, NETs represent relatively recent clinicopathologic entities. As a consequence, their management has evolved over the last decade based on increased understanding of their tumor biology and molecular regulation. Given the diverse appreciation of the disease complexity, a variety of different sequences of diagnostic and therapeutic procedures has being proposed and debated in individual medical centers.[10] Key issues involved in the development of an optimal management strategy include the precise type of the tumor, the grade and stage of the lesion, and the overall patient's general condition. Ideally, removal of the primary tumor should be initially undertaken and, thereafter, appropriate strategies should be developed for the management of residual disease. It is the latter issue that often evokes controversial discussion because there exists a paucity of rigorous

prospective randomized trials to support a clearly defined therapeutic strategy. In most cases, therefore, the therapeutic strategy is usually determined by discussion based on experience and institutional bias.[10] Although a variety of management guidelines have been developed, they tend to vary from country to country. The most significant limitation of the published recommendations is that, in most circumstances, they are based on low-grade evidence obtained from retrospective studies of heterogeneous patient and tumor populations.[4]

In principle, however, the choice of therapy depends on the primary therapeutic aim for a particular individual, which may range from an attempt at complete surgical eradication of the disease to amelioration of symptoms. In most circumstances, complete removal of disease is impossible because of a late clinical presentation with evidence of metastatic progression (Fig. 2). The latter may be local or more commonly involves hepatic metastasis and occasionally spread to bone, lungs, and even brain. Thus, for practical clinical purposes, most therapy is deployed toward decreasing the size of metastatic lesions, reducing metastatic growth, and ameliorating symptoms (in functional lesions).[11] To achieve these goals, a wide variety of therapeutic strategies have been developed. The surgical options include resection of the primary, hepatic metastases resection, radiofrequency ablation, and even hepatic transplantation.[12] Interventional radiology techniques include embolization of hepatic metastases (with or without cytotoxic agents) or the use of radioactive microspheres. Medical therapy ranges from the use of bioactive agents such as somatostatin analogues or interferon to standard chemotherapy. More recently, a variety of novel molecular targeted agents, including Everolimus, Sunitinib, and Bevacuzimab, have been used with marginal efficacy.[13] Of particular interest has been the development of targeted radiotherapy using a variety of different isotopes, including indium, yttrium, and lutetium.[14] This novel therapeutic strategy, delivered by intravenous infusion, has been designated peptide receptor radionuclide therapy (PRRT) (Fig. 3).

NON-SOMATOSTATIN-BASED THERAPIES

Medical Therapy

In general, the type of therapy used depends on the grade and proliferation of the tumor. High-grade, rapidly proliferating lesions, especially

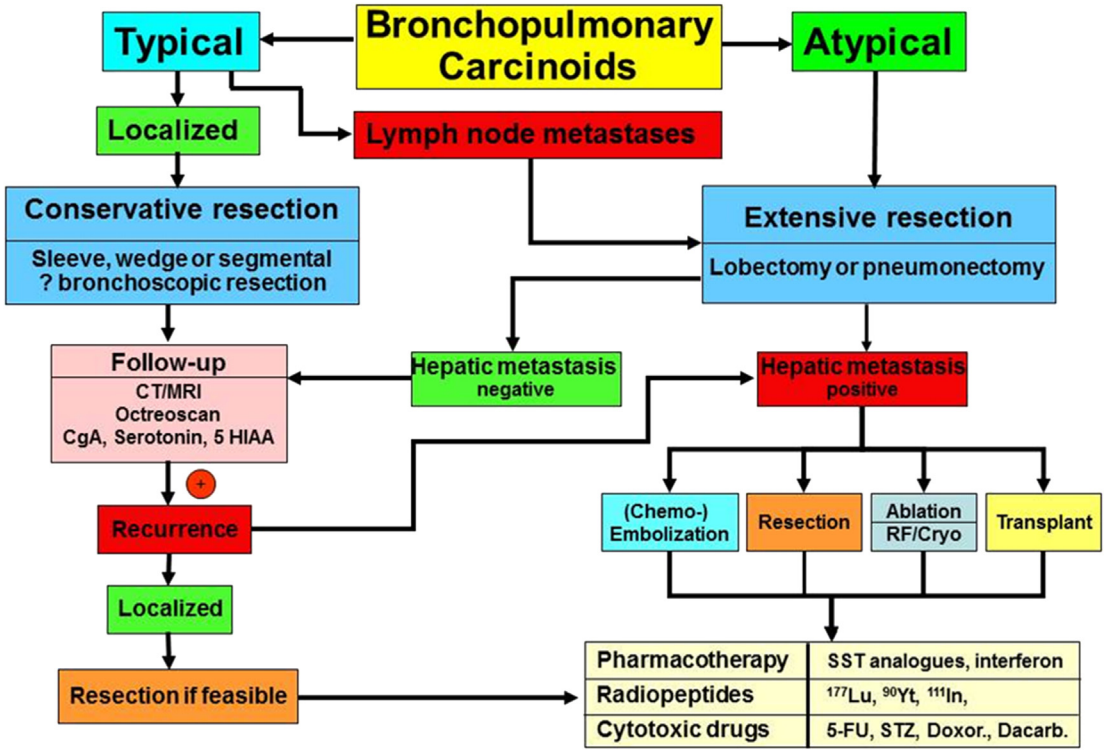

Fig. 2. Treatment options in bronchopulmonary NETs, including both typical and atypical carcinoids. The management of metastatic or unresectable disease comprises locoregional strategies as well as systemic treatments, including PRRT.

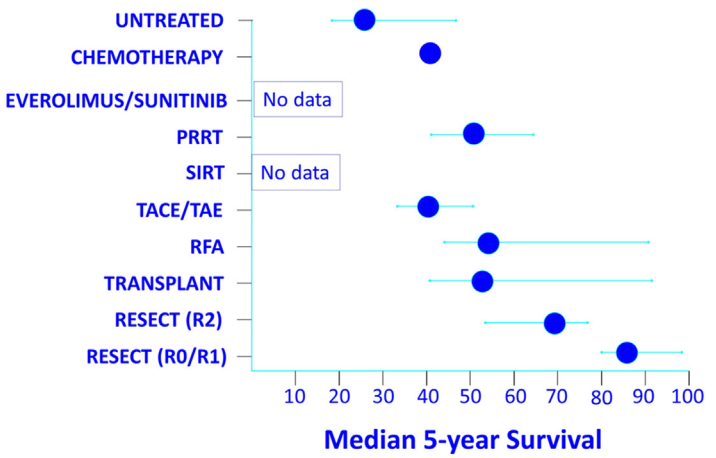

Fig. 3. Treatment outcomes for NETs. Therapy-related survival is the highest in resectable tumors. At diagnosis, 40% to 95% of tumors have already metastasized (depending on location of the primary lesion). PRRT compares well with other techniques, including locoregional approaches and chemotherapy. Toxicity is a major adverse event in the latter category of therapy.

from the pancreas (NEC G3), are amenable to chemotherapy, whereas "targeted" therapies (eg, Everolimus or Sunitinib) and biotherapy (eg, somatostatin analogues or interferon) are used in "slower" growing lesions (NET G1 or G2). Chemotherapy has greater objective response rates (35%–40%) in pancreatic NETs than Everolimus or Sunitinib.[15] The molecular markers that identify patients who would optimally benefit from individual or combinations of therapies, apart from somatostatin receptor expression, are currently unknown. For chemotherapy (including 5-fluorouracil, doxorubicin, and streptozotocin), the volume of LM is the most significant predictor of outcome and directly correlates with progression-free survival (PFS). Potential problems with chemotherapy include cumulative risks of nephrotoxicity/myelosuppression and systemic adverse events.[16] For targeted therapies, there is evidence to suggest a specific use in NE LMs. In the Everolimus study in pancreatic NETs, 92% of whom had NE LMs, the agent was associated with improved PFS (6.4 months compared with placebo), an effect that was long lasting (35% stable at 18 months). Tumor remissions were, however, rare (5%). In the Sunitinib study (95% of pancreatic NETs had distant metastases including NE LMs), a significant PFS prolongation (5.9 months compared with placebo) was achieved with tumor remissions of less than 10%. There is no evidence for use of Sunitinib or Everolimus in LM of intestinal origin. For biotherapies, there is a modest amount of data for interferon, but for somatostatin analogues, the Placebo controlled, double-blind, prospective, Randomized study on the effect of Octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine MIDgut tumors (PROMID) study on small bowel NETs suggested that any benefit from these agents was defined by the extent of liver involvement. Thus, individuals with less than 10% involvement had better PFS than those with greater than 10% involvement. In summary, 3 prospective randomized trials provide only marginal evidence for the efficacy of these agents (Everolimus and Sunitinib) in the treatment of NE LMs.

Angiographic Liver-directed Techniques

Liver-directed intra-arterial therapies available in the treatment of unresectable NE LMs include trans-arterial embolization (TAE), transarterial chemoembolization (TACE), and selective internal radiotherapy (SIRT) with Yttrium-90 (^{90}Y) microspheres. For TAE or TACE, symptomatic responses have been reported in 53% to 100% of patients (10–55 months) and morphologic responses were noted in 35% to 74% (6–63 months) with a PFS of ~18 months with 5-year survivals of 40% to 83%. Mortality and morbidity, including postembolization syndrome, varied between 0% to 5.6% and 28% to 90%, respectively; TAE appears to be superior to TACE for small bowel NETs. In a recent multicenter report on SIRT, stable disease by imaging was achieved in 22.7%, a partial response in 60.5%, and complete response in 2.7%. A median survival of 70 months was reported with progressive disease evident in 4.9%. The most frequently observed clinical toxicities were fatigue and nausea (occurring in <10%). In an international multicenter prospective treatment registry to investigate the safety and efficacy of hepatic artery therapy for primary or secondary liver tumors, response rates for SIRT and TACE were comparable at 6 months in a group of 43 patients with comparable NE LM disease. At 12 months, however, a significantly lower response rate was

observed in the SIRT group: 46% versus 66%. Although SIRT may have advantages over TAE/TACE in terms of reduced adverse effects and the requirement for fewer treatments, it can be associated with side effects in terms of radiation gastritis, duodenal ulceration, and sclerotic alteration of healthy liver parenchyma. SIRT is also relatively expensive and patients require careful selection because lung shunting may be an issue. It is clear that more long-term outcome data are required to assess the efficacy of SIRT.

SOMATOSTATIN ANALOGUE-RELATED THERAPIES

"Cold," non-radiolabeled, somatostatin analogues exhibit significant effects in terms of ameliorating symptoms. The various synthetic peptide analogues each have different binding properties to the 5 somatostatin receptor subtypes. Generally, however, they represent an effective class of agents that inhibit peptide secretion from NET cells with relatively few and limited adverse events.[17] This is particularly evident in small bowel NETs, which often exhibit severe flushing and diarrhea. Similar positive effects are evident in functional pancreatic NETs, such as glucagonoma and VIPoma. Unfortunately, administration requires monthly injections, which are inconvenient and often painful. Furthermore, the beneficial pharmacologic effects are not always sustained (breakthrough) because of either tachyphylaxis or increasing production of bioactive products by an advancing tumor.[18] It has been proposed that cold somatostatin analogues decrease proliferative activity of NETs. The evidence for this assertion is, however, neither rigorous nor robust and, if such an effect is present, it is only evident in a small minority of lesions.[19,20]

PRRT with radiolabeled somatostatin analogues is an innovative treatment of inoperable or metastasized, well/moderately differentiated, NETs, particularly of the GEP (and of the lung).[21] Somatostatin analogues represent, to date, the prototype and the most successful paradigm of radiopeptide therapy. This successful paradigm of radiopeptide therapy reflects the development of a synthetic peptide analogue, octreotide, and its variants, using the native somatostatin molecule as a base. Overall, the therapeutic efficacy of somatostatin analogues and, subsequently, of their radiolabeled counterparts, is due to their high affinity for somatostatin receptors subtype 2 (S2) and moderate affinity for subtype 5 (S5) and is consistent with the prevalent overexpression of S2 and S5 in most NETs.[22]

PRRT Background

The rational scientific PRRT basis relies in the presence of a somatostatin receptor on the surface of NETs to which an isotopically labeled radiopeptide is directed. The subsequent cellular radiopeptide internalization thereafter delivers the radioactivity directly into the intracellular compartment of the tumor (**Fig. 4**). The clinical process of PRRT consists in the systemic administration of a suitably radiolabeled synthetic

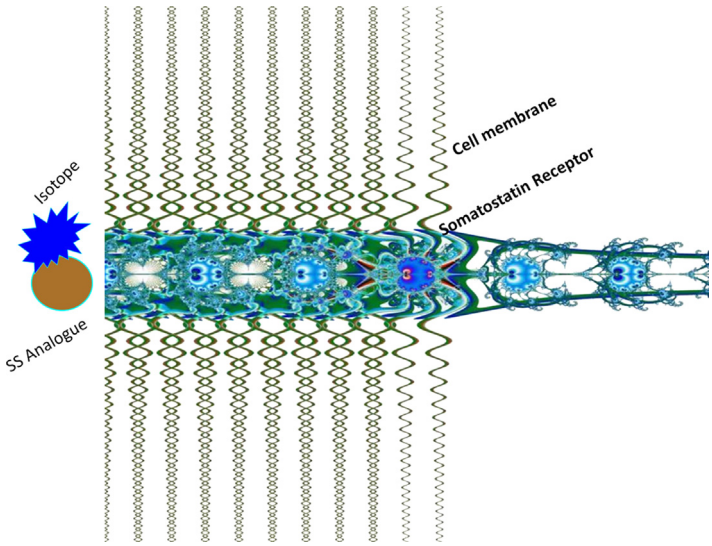

Fig. 4. Mechanism of effectiveness of PRRT. After the somatostatin (SS) analogue linked to the isotope binds to the membrane somatostatin receptor, the radiopeptide/somatostatin receptor complex is internalized. Thus, radioactivity is transported into the intracellular receptor recycling compartment of the NET cell, where it exerts its action in proximity to the nucleus.

somatostatin analogue, fractionated in sequential cycles (usually 4–5) every 6 to 9 weeks, until the intended total amount of radioactivity has been delivered. The precise amount administered depends mainly on the limitations imposed by renal irradiation and to a lesser extent on bone marrow.

PRRT was introduced into clinical practice in 1994. It represented a logical step following the initial development of the diagnostic technique for in vivo localization of NETs using the radiolabeled somatostatin analogue [^{111}In-DTPA0-D-Phe1]-octreotide or ^{111}In-pentetreotide.[23] Thus, the same principle was used, but increased isotope activity (high-dose ^{111}In-pentetreotide) provided a therapeutic as opposed to a diagnostic benefit. Therapeutic efficacy reflects the activity of the Auger and conversion electrons emitted by ^{111}In. Despite the theoretical considerations, partial remissions remained rare.[24] As a consequence of these relatively disappointing results, isotopes with higher energy and longer range, such as the pure β emitter ^{90}Y, were considered more appropriate for therapeutic evaluation. The β particles emitted by ^{90}Y (maximum energy 2.27 MeV, penetration range $R_{\beta max}$ 11 mm, half-life $T_{1/2}$ 64 hours) are advantageous, allowing simultaneously a direct killing of somatostatin receptor-positive cells and a cross-fire effect that targets nearby receptor-negative tumor cells. To facilitate efficacy further, novel octreotide analogues were developed. Thus, for ^{90}Y, a new analogue, Tyr^3-octreotide, with a similar pattern of affinity for somatostatin receptors, was developed at the University of Basel. This analogue was characterized by high hydrophobicity, ease of labeling with ^{111}In and ^{90}Y, and tight binding to the bifunctional chelator DOTA, which securely encloses the radioisotope (1,4,7,10-tetra-azacyclododecane-*N*,*N*′,*N*″,*N*‴-tetra-acetic acid).[25,26]

[^{90}Y-DOTA^0,Tyr^3]-octreotide or ^{90}Y-DOTATOC or ^{90}Y-octreotide was initially used in the treatment of metastatic NETs in 1996. The excellent symptomatic and objective response following several cycles of ^{90}Y-octreotide therapy encouraged further studies to examine the potential of PRRT in NET disease.[27] As a consequence of the positive experience with ^{90}Y-octreotide, it became the most used radiopeptide in the first decade of PRRT experience.[14,28–31]

Since 2000, however, a more effective analogue, octreotate (Tyr^3, Thr^8-octreotide), with 6-fold to 9-fold higher affinity for somatostatin S2 has been used. The chelated analogue [DOTA]^0-Tyr^3-octreotate or DOTATATE can be labeled with the β-γ emitter Lutetium-177 ($E_{\beta max}$ 0.49 MeV, $R_{\beta max}$ 2 mm, $T_{1/2}$ 6.7 days) and has been investigated in several clinical phase I and II studies (Fig. 5).[14,32–34] ^{177}Lu-octreotate has subsequently become one of the most frequently used radiopeptides for PRRT; this has been particularly evident in recent years given its efficacy, tolerability, and manageability. ^{177}Lu-octreotate is currently being evaluated in a randomized phase III registration trial in small bowel NETs.

PRRT Clinical Protocol

Candidates for PRRT with radiolabeled somatostatin analogues are individuals with tumors that exhibit a significant somatostatin receptor overexpression. A key issue in the inclusion criteria is that the somatostatin receptors should be functional, namely, be able to internalize the receptor-analogue complex and retain the radioactivity inside the cell. Thus, the critical issues for effective therapy remain the somatostatin receptor overexpression and the evidence of functionality.

To be considered appropriate candidates for therapy, individuals should be selected based on scintigraphy with ^{111}In-pentetreotide (or, more recently, receptor positron emission tomography [PET] with ^{68}Gallium-labeled octreotide). Such images should indicate an adequate uptake (at least equal to the uptake of normal liver) as evidence of adequate expression of targetable somatostatin

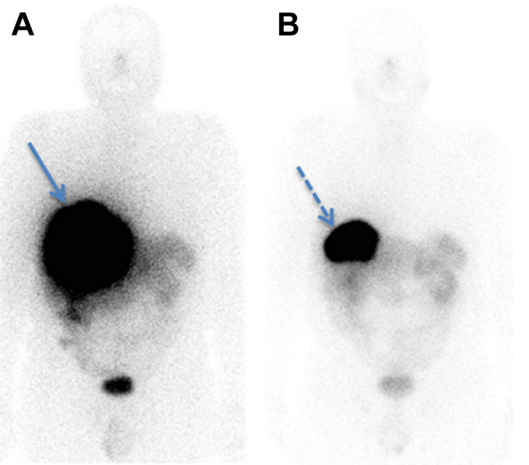

Fig. 5. Objective response to ^{177}Lu-octreotate PRRT in an unresectable rectal NET with hepatic metastasis (*A*) basal ^{177}Lu-octreotate scan (*solid arrow*). The patient underwent a prior rectosigmoid resection and exhibited disease progression following chemotherapy with capecitabine. (*B*) The final ^{177}Lu-octreotate scan after 8.6 GBq of ^{177}Lu-octreotate. Evidence of a partial objective response (*dashed arrow*) enabled subsequent embolization followed by a multidisciplinary treatment sequence plan.

receptors; this is necessary to ensure and calculate an appropriate high tumor dose with low exposure to normal tissues that express physiologic levels of somatostatin receptors.[35]

Scintigraphic or PET tomoscintigraphic evaluation is to date the most accurate noninvasive method to identify and confirm the overexpression of functioning receptors. An alternative strategy is to use immunohistochemistry, which provides similar information at the time of biopsy. Immunohistochemistry, however, is not as quantitatively accurate as molecular analysis (polymerase chain reaction and Western blot), which can precisely define the level of somatostatin receptors and their functionality.[36] Optimally, the use of in vivo functional scintigraphic or PET methods facilitates the simultaneous evaluation of the receptor density and the internalization capacity in real-time in all lesions.

When evaluating a receptor scan to determine PRRT selection, it is important to exclude false positives. For the most part, these represent accumulations of inflammatory cells, which express somatostatin receptors. False positives include gallbladder (inflammation), accessory spleens, recent surgical scars (inflammatory infiltrate), previous radiotherapy, and any other cause of granulomatous-lymphoid infiltrate that can mimic the presence of NET tissue.

Potential causes of false negatives should also be considered. These false negatives are mainly represented by small, subcentimeter lesions, under the resolution limit of the instrument (although this limitation is partially overcome by receptor PET/computed tomography). In addition, certain tumors, especially benign insulinomas and most highly malignant NETs, do not express adequate somatostatin receptors for detection.

PRRT Technique

PRRT consists of the cyclical systemic administration of the radiopeptide. The cumulative activity, fractionated in multiple cycles, is able to irradiate the tumor efficiently, without surpassing the conventional 25- to 27-Gy absorbed dose threshold to the kidneys, which are the dose-limiting organs. Recently, it has been reported that the biologic effective dose (BED) as opposed to the absorbed dose provides a dose threshold value that is slightly higher.[37] The rhythm of fractionation, every 6 to 9 weeks, is based on the time that has been determined as necessary to recover from possible hematological toxicity.

To diminish the renal dose of irradiation, patients are premedicated with an intravenous infusion of positively charged amino acids (lysine or arginine) in the amount of at least 25 g per day. This infusion is started 2 to 3 hours before the isotope administration and is maintained until 2 to 3 hours following cessation of the isotope infusion. The infusion has the objective of simultaneously hydrating the patients and reducing the renal radioactivity dose by providing competitive inhibition of the proximal tubular reabsorption of the radiopeptide. The radiopeptide is intravenously administered slowly over 20 minutes in approximately 100 mL of saline. In some circumstances, mild adverse events are experienced during the infusion. These mild adverse events include gastrointestinal symptoms, such as a slight nausea, and occasionally, emesis. These symptoms may be related to the amino acid coadministration, but are easily controlled with appropriate medication.[21]

PRRT Efficacy

In almost 2 decades of clinical application, PRRT with ^{90}Y-octreotide or ^{177}Lu-octreotate has provided effective clinical therapy as indicated by tumor responses, symptom relief, and QoL improvement as well as a decrease in biomarker levels and enhanced survival (see **Fig. 5**). Several clinical phase I–II trials indicate that radiolabeled somatostatin analogue PRRT is among the promising newly developed targeted tools in NETs, with registered objective responses in more than 30% of individuals, mainly of GEP origin.[14,31,33,35,38–40]

PRRT and Bronchopulmonary NETs

Although bronchial NETs overall represent the second most common type of NET among differentiated histologic types, there have been few, dedicated PRRT trials. The PRRT data for bronchopulmonary NETs are therefore typically extrapolated from more general studies (**Fig. 6**).

In the first decade of experience, ^{90}Y-octreotide was the most commonly used radiopeptide. However, all the published results derive from different phase I–II studies performed independently by a variety of centers. As a consequence, information is heterogeneous as to inclusion criteria and specific treatment schemes. A rigorous direct comparison is therefore virtually impossible at this time. Nevertheless, despite these limitations, objective responses have been documented in 10% to 34% of patients (**Table 1**).[14,29,30,39–42]

Current isotope administration protocols schedule the injection of standard radioactivities that were established based on previous dose escalation studies as well as clinical experience. This practice has resulted in substantial differences among protocols, as to activities, which may be fixed or related to body weight or surface,

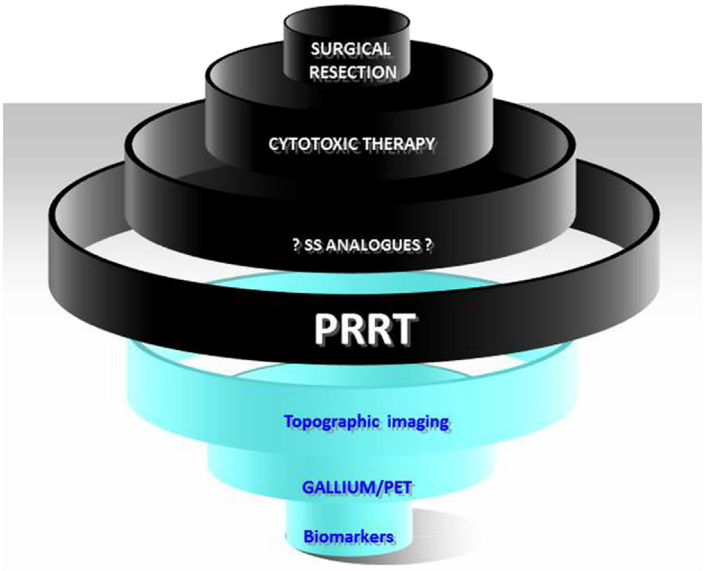

Fig. 6. Role of diagnostic and therapeutic tools in the management of bronchopulmonary NETs ranging from surgical resection to PRRT.

number of cycles, and time intervals between cycles.

The initial studies with ^{90}Y-octreotide were undertaken in individuals with very advanced disease. However, the documented effectiveness of the therapy, even in these situations, led to the usage of PRRT in earlier phases of disease because it was evident that with decreased tumor burden radiopeptides exhibited a greater efficacy. The rationale for this strategy was provided by numerous factors including tumor volume and the biologic features of the neoplasm. Thus, more advanced (aggressive) tumors expressed less somatostatin receptors, increased genetic mutations, such as in p53,[43] and are thus less responsive to treatment. Key issues in predicting optimal PRRT outcome were tumor load, especially in the liver, and performance status. Evaluation of such indices of prognosis and outcome concluded that treatment in a phase of "early" progression rather than a "wait-and-see" approach was advantageous. Overall, it was apparent that PRRT treatment in advanced stage disease was substantially less effective. A further consideration was the type of disease being treated. Thus, metastases of pancreatic NETs were frequently more amenable to therapy compared with other types of NETs. NETs that were active secretors of bioactive agents (functional) also tended to relapse very rapidly.[44]

Table 1
Clinical results of PRRT with either ^{90}Y-octreotide or ^{177}Lu-octreotate in GEP-NETs

Ligand (Ref.)	Patient Number	CR + PR (%)	Response Criteria	Outcome (mo)
^{90}Y-octreotide[41]	23	13	WHO	Not assessed
^{90}Y-octreotide[57]	37	27	WHO	TTP >26
^{90}Y-octreotide[45]	36	34	WHO	Not assessed
^{90}Y-octreotide[28]	21	29	WHO	TTP 10
^{90}Y-octreotide[42]	58	9	SWOG	TTP 29
^{90}Y-octreotide[30]	90	4	SWOG	PFS 16
^{90}Y-octreotide[40]	53	23	WHO	PFS 29
^{90}Y-octreotate[39]	58	23	WHO	PFS 17
^{177}Lu-octreotate[33]	310	29	SWOG	PFS 33
^{177}Lu-octreotate[34]	42	31	RECIST	TTP 36
^{177}Lu-octreotate[52]	52	39	SWOG	PFS 29

In a study carried out at Basel University, 39 patients with NETs, mostly of GEP origin, were treated with 4 cycles of ^{90}Y-octreotide, with a cumulative activity of 7.4 GBq. Objective responses, according to World Health Organization (WHO) criteria, were described in 23%, with a complete remission in 2 patients, a partial response in 7 patients, and a disease stabilization in 27 patients. Pancreatic NETs (13 patients) showed a better objective response (38% partial + complete) than other tumor types. A significant related-symptoms amelioration occurred in most patients. In this series, 3 patients with progressive bronchial tumors were also included. All demonstrated disease stabilization after PRRT.[45]

In a multicenter phase I study, carried out in Rotterdam, Louvain, and Tampa, 60 patients with GEP-NETs were treated with 4 cycles of 0.9, 1.8, 2.8, 3.7, 4.6, and 5.5 GBq/m^2 of ^{90}Y-octreotide administered at 6 to 9 weekly intervals. In an initial evaluation of the results (2002) in 32 evaluable patients, objective responses (according to Southwest Oncology Group [SWOG] criteria) were evident. These responses constituted ~9% partial responses and 9% minor responses.[46] In a subsequent reanalysis of 58 assessable patients of the same population who were treated with cumulative activities of 1.7 to 32.8 GBq, a 57% clinical benefit, including stabilization and minor responses (SWOG criteria), was observed. Objective responses were described in 5%. The most relevant finding of the study was the observed overall survival, with a median value of about 37 months and a median PFS of about 29 months. These results compared well with the 12-month overall survival of a historical group treated with ^{111}In-pentetreotide. The median PFS in this group was 29 months. Characteristically, patients stable at baseline had a better overall survival than those who were progressive at baseline. The extent of disease at baseline was also a predictive factor for survival.[42]

The results of 2 phase I–II studies and a retrospective evaluation in 141 patients were published by the Milan group in 2004. Somatostatin receptor-positive tumors, mainly gastroenteropancreatic and bronchial NETs, were treated with a cumulative activity of 7.4 to 26.4 GBq of ^{90}Y-octreotide, divided into 2 to 16 cycles, administered 4 to 6 weeks apart. The objective response rate was 26%, including partial and complete responses (SWOG criteria). Disease stabilization was observed in 55% and disease progression in 18%. The mean duration of response ranged from 2 to 59 months (median 18). Most who responded had GEP-NETs. A significant observation was that assessment of the objective response according to the basal status indicated that individuals stable at baseline demonstrated a better outcome (partial and complete responses in 32%) than individuals with progressive disease (partial and complete responses in 24%). In this series, 11 patients with bronchial tumors were included. Ninety-one percent were in progression at enrollment and were treated with standard courses of PRRT, with cumulative activities ranging from 8 to 22.5 GBq. After completion of the treatment, 1 patient had a partial remission and 8 patients showed stabilization of disease (SWOG criteria). In an earlier escalation study published by the same group in patients with somatostatin-positive tumors (mainly in progression), 3 patients with bronchial NETs were included, with resulting stability and partial remission in 2 patients.[28,29]

A multicenter study published by Bushnell and colleagues[30] in 2010 evaluated the role of ^{90}Y-octreotide in 90 patients with symptomatic, metastatic “carcinoids” (small bowel NETs). The data indicated stabilization of tumor response (SWOG criteria) in 74% as well as a durable amelioration of symptoms related to the tumor mass and the hypersecretion of bioactive amines. This trial reported a PFS of 16 months and an overall survival of 27 months.

More recently, the Basel group published the results of an open-label phase II trial in 1109 patients treated with ^{90}Y-octreotide, divided into multiple cycles of 3.7 GBq/m^2 each. Objective morphologic responses (Response Evaluation Criteria In Solid Tumors [RECIST] criteria) were observed in 378 (34.1%), biochemical responses in 172 (15.5%), and symptomatic responses in 329 (29.7%). In this series, the NET groups were 265 small bowel, 84 bronchial, and 342 pancreatic tumors. The rates of objective response were 26.8%, 28.6%, and 47%, respectively. A longer survival was correlated with tumor and symptomatic response. The best predictor of survival, however, was the tumor uptake at baseline.[31] Protocols combining ^{177}Lu-peptides and ^{90}Y-peptides have been recently considered to take advantage of the different physical properties of both 2 radionuclides. In theory, the combination of the 2 radioisotopes would allow simultaneous treatment of both larger lesions (based on the higher energy and penetration range of the particles emitted by ^{90}Y) and small lesions (based on the lower energy and penetration range of ^{177}Lu). This strategy, however, must still be validated in clinical practice in larger series. Furthermore, the previously published studies include treatment schemes wherein ^{177}Lu and ^{90}Y were administered using empirically designed protocols rather than

being based on individualized dosimetric analyses.[47,48] The results of PRRT performed in a Danish cohort of 69 patients treated in Basel with different combinations of Y-peptides and/or Lu-peptides were recently published. Complete response was evident in 5 cases (7.4%), a partial remission in 11 cases (16.2%), and stability in 42 cases (61.8%). The median PFS was 29 months. Pancreatic NETs responded better than those with small bowel tumors. Six patients with bronchial NETs were included: one exhibited a partial remission and 3 were stable.[40] Experience has also been obtained from studies with ^{90}Y-DOTATATE. A group of 60 patients with histologically proven GEP-NETs were treated with 4.1 to 16.2 GBq per patient (mean 3.7 GBq per therapy) in 1 to 3 cycles. Six months after PRRT completion, a partial response was evident in 13 patients (23%), whereas the remaining had stable disease (77%). The median PFS was 17 months and the median overall survival was 22 months. Hematological toxicity WHO grades 3 and 4 were noted during therapy in 10%, which persisted in 5%. After 24 months of follow-up, renal toxicity grade 2 was seen in 7 (11.6%) and the authors emphasized the need for careful renal monitoring.[39] The novel radiopeptide DOTATATE labeled with ^{177}Lutetium, ^{177}Lu-DOTATATE, or ^{177}Lu-octreotate attained great popularity since its introduction in clinical trials in 2000, reflecting its higher affinity for somatostatin S2, its easier manageability, a lower dosimetric burden on the kidney, and the possibility of obtaining scintigraphic images and dosimetric studies at the same time, owing to the γ photon coemission of ^{177}Lu. It is currently therefore the most commonly used radiopeptide for PRRT. The initial clinical trials were undertaken at Rotterdam University. In a preliminary report, 35 patients with GEP-NETs were treated with 3.7, 5.6, or 7.4 GBq of ^{177}Lu-octreotate, up to a final cumulative dose of 22.2 to 29.6 GBq, with complete and partial responses in 38% (WHO criteria). No serious side effects were observed.[49] In a subsequent amplification of this series, 131 patients with somatostatin receptor–positive GEP-NETs were treated with cumulative activities of ^{177}Lu-octreotate ranging from 22.2 to 29.6 GBq. In the 125 evaluated patients (SWOG criteria), a complete remission was observed in 3 patients (2%), a partial remission in 32 patients (26%), minor responses in 24 patients (19%), and stable disease in 44 patients (35%). Twenty-two patients (18%) progressed. Better responses were more frequent in individuals with a high uptake on baseline ^{111}In-pentetreotide scintigraphy and those with limited liver involvement. Conversely, progression was significantly more frequent with a low performance score and extensive disease at enrollment. Median time to progression was greater than 36 months, comparing favorably to chemotherapy.[44] In addition, ^{177}Lu-octreotate treatment of metastatic GEP-NETs was also associated with a significant improvement in the global health/QoL on various symptom scales, particularly fatigue, insomnia, pain, as well as role, emotional, and social functions. The effect was more frequent in individuals with tumor regression, but, surprisingly, it was also evident in those with progressive disease.[50] Of note was the observation that there was no significant decrease in QoL in patients who were asymptomatic before therapy.[51] Recently, an evaluation of an enlarged series of 504 patients treated with ^{177}Lu-octreotate, 310 of which were evaluated for efficacy, confirmed the occurrence of complete and partial remissions in 2% and 28%, with minor responses in 16% and stability in 35%, respectively (SWOG criteria). However, the most significant information derived from this study was the impact of PRRT on survival, with a median overall survival greater than 48 months and a median PFS of 33 months. A direct comparison with data obtained from similar patients (in the literature) showed a substantial 40-month to 72-month survival benefit for PRRT-treated individuals. Although these data are not derived from robust/rigorous prospective randomized phase III trials, this substantial survival difference in all probability reflects a real impact of PRRT as a therapeutic modality. These PRRT data compare favorably with other treatments, such as chemotherapy, from both the cost/benefit and the tolerability point of view.[33] A categorization of objective response once again indicated that pancreatic NETs tended to respond better than other GEP-NETs, although functioning tumors (eg, pancreatic gastrinomas) tended to relapse in a shorter interval (median time to progression 20 months vs >36 in the remaining GEP-NETs).[44]

A cohort of 51 patients with unresectable/metastatic NETs, mainly of GEP origin, was treated in a phase I–II study aimed at defining toxicity and efficacy of ^{177}Lu-octreotate. Patients were divided into 2 groups, receiving escalating activities, from 3.7 to 5.18 GBq and from 5.18 to 7.4 GBq, with cumulative activities up to 29 GBq, based on dosimetry. Partial and complete responses were observed in 15 patients (32.6%). The median time to progression was 36 months, with an overall survival of 68% at 36 months. Nonresponders and patients with extensive tumor involvement had a lower survival.[34] A recent prospective phase II study included a cohort of 52 patients with advanced well/moderately differentiated pancreatic NETs who were treated with ^{177}Lu-octreotate.

According to the absence or presence of risk factors for renal toxicity, such as hypertension or diabetes, patients were divided into 2 groups and treated with different levels of activity, full dose (21–28 GBq) compared with a reduced dose (11–20 GBq), respectively. Both regimens resulted in antitumor activity. However, PFS was not reached at the time of the analysis in the cohort treated with the full-dose regimen, whereas it was 20 months in those treated with reduced doses, suggesting the former scheme should be recommended, whenever possible.[52] A phase II study was performed in individuals with "poor responding" tumors, including bronchial and gastric NECs. Patients were treated with standard 22.2-GBq to 29.6-GBq activities. Despite the limited numbers studied, the observed objective response (SWOG criteria) was comparable to GEP-NETs. The bronchopulmonary NETs results were 5 partial responses, 1 minor response, and 2 stabilizations in 9 patients. In the gastric tumor group, there was 1 complete response, 1 minor response, and 2 stabilizations (5 patients). In thymic tumors, the series was too small to draw any conclusions. The authors concluded that, contrary to previous findings, PRRT was as effective in bronchial and gastric NETs as in GEP-NETs.[53]

A recent study using a salvage protocol with ^{177}Lu-octreotate was published by the Rotterdam group. Patients in progression were enrolled after an initial response to PRRT with ^{177}Lu-octreotate, administered using standard cumulative activities (22.2–29.6 GBq). In this series, 32 patients with bronchial or GEP-NETs received 2 additional cycles of ^{177}Lu-octreotate, with a cumulative activity of 15 GBq. A new objective response occurred in 8 patients (2 partial and 6 minor responses), whereas stabilization was identified in another 8. Median time to progression was 17 months. Both response rate and duration over time appeared lower than during the primary treatment. Nevertheless, this "salvage therapy" was well tolerated by most patients and should be considered a valuable option for this category of patient.[54] In more recent times, in keeping with recent tendencies in oncology, PRRT experiences have been focused toward combination therapies. In particular, combinations of the radiosensitizer chemotherapy agent, capecitibine, with ^{177}Lu-octreotate have been undertaken. An initial study in a small group (n = 7) with progressive GEP-NETs reported encouraging results.[55] Patients were treated with 4 cycles of standard activities of ^{177}Lu-octreotate followed by capecitabine (1650 mg/m^2) for 2 weeks. No severe toxicity, particularly hand-foot syndrome or hematological/renal-associated toxicity, was evident. Objective responses were observed. A recent phase II study of progressive NETs (n = 35) was reported.[56] Patients were treated with 4 cycles of 7.8 GBq of ^{177}Lu-octreotate followed by capecitabine, 1650 mg/m^2 (2 weeks). A 24% objective response with a 70% stable disease and 6% progression without adjunctive toxicity (RECIST criteria) was observed.

PRRT Safety Profile

After 18 years of experience, it is apparent that, from the safety perspective, PRRT with either ^{90}Y-peptides or ^{177}Lu-peptides is generally well-tolerated. Acute side effects are usually mild with some of them related to the co-administration of amino acids (including nausea, and rarely, emesis). Others are related to the radiopeptide, such as fatigue (common), or the exacerbation of an endocrine syndrome, which may rarely occur in the treatment of functional tumors. Chronic and permanent effects on target organs, particularly the kidneys and the bone marrow, are generally mild if the necessary precautions, such as fractionation and attention to specific risk factors, are undertaken (**Table 2**).[31,35,40,45,57] In this

Table 2
Long-term toxicity after PRRT with either ^{90}Y-octreotide or ^{177}Lu-octreotate in GEP-NETs

Ligand (Ref.)	Patient Number	Follow-Up (mo)	Renal Toxicity (Creatinine)	MDS	Leukemia
^{90}Y-octreotide[57]	41	15	0	0	0
^{90}Y-octreotide[45]	39	6	3% Grade 2	0	0
^{90}Y-octreotide[28]	40	19	10% Grade 1	0	0
^{90}Y-octreotide[42]	58	18	3% Grade 4	1	0
^{90}Y-octreotide[40]	53	17	0	1	0
^{90}Y-octreotide[31]	1109	23	9.2% Grade 3/4[a]	1	1
^{177}Lu-octreotate[33]	504	19	0.4% Grade 4	3	0
^{177}Lu-octreotate[34]	51	29	24% Grade 1	0	0

[a] Toxicity grade measured on glomerular filtration rate.

respect, it is apparent that, using appropriate dosimetry, it is possible to deliver elevated absorbed doses to the tumor, with relative sparing of healthy organs, such as the kidneys and the bone marrow (Table 3).

Although acute hematological toxicity is usually mild and transient, permanent and severe bone marrow toxicity may be a rare event after PRRT, as bone marrow–absorbed doses are usually below the threshold of toxicity.[58] Delayed renal toxicity that may occur if the dose threshold is exceeded is permanent. The kidneys, as a consequence of their marked radiosensitivity, represent the critical organs, especially for ^{90}Y-peptides administration. Renal irradiation derives from the reabsorption of the radiopeptides at the site of the proximal convoluted tubules, with a subsequent accumulation in the renal interstitium, where the radioactivity exerts its action. Studies with external radiotherapy indicate a threshold of tolerance in the range of 23 to 27 Gy.[59] The recently introduced BED concept appears more accurate in predicting toxicity and thus represents a more universal cipher to express radioactive dosage, irrespective of the modality of delivery. The use of this parameter indicates that the renal threshold for toxicity after PRRT is approximately 40 Gy.[60,61] A critical issue in ameliorating renal toxicity is provided by the strategy of co-infusing positively charged amino acids, such as lysine or arginine. These amino acids competitively inhibit radiopeptide reabsorption with a consequent 9% to 53% reduction of the renal radioactivity dosage.[62,63] Despite renal protection, a generally mild loss of renal function occurs, with a median decline in creatinine clearance of 7.3% per year for ^{90}Y-octreotide and a median 3.8% per year for ^{177}Lu-octreotate.[64] Nevertheless, instances of severe, end-stage, renal damage are currently extremely rare. Previous instances, for the most part, represent residual events that occurred during the early usage of ^{90}Y-peptide PRRT, when administration used very high activities in the absence of renal protection.[65]

In recent times, it has become apparent that a higher and more persistent decline in creatinine clearance with the subsequent development of renal toxicity is more likely to occur in individuals with pre-existent risk factors for delayed renal toxicity. These risk factors include long-standing and/or poorly controlled diabetes and hypertension. PRRT with ^{90}Y-peptides in particular seems more frequently associated with a reduction of renal function; presumably, this reflects the physical characteristics of the radioisotope. In a long-term evaluation of renal toxicity after PRRT in a group of 28 patients undergoing PRRT with dosimetric analysis, 23 of whom were treated with ^{90}Y-octreotide, a low, 28-Gy BED threshold was observed in patients with risk factors (mainly hypertension and diabetes), in comparison to 40 Gy in individuals without such risk factors.[66]

In a retrospective series of 1109 patients treated with ^{90}Y-octreotide, 103 subjects (9.2%) experienced grade 4 to 5 permanent renal toxicity.[31] Multivariate regression revealed that the initial kidney uptake was predictive for severe renal toxicity. However, it seems likely that this relatively high incidence of renal toxicity is related to the high administered activities per cycle (3.7 GBq/m^2 body surface, namely, activities of about 6.4 GBq per cycle in a standard man) and to the fact that individuals with pre-existing impairment of renal function were not excluded from PRRT. A further consideration is that routine infusion of protective amino acids was not used in the earlier component of the study.[65] From a hematological point of view, PRRT is generally well tolerated. Severe, WHO grade 3 or 4, toxicity occurs in less than 13% after

Table 3
Mean absorbed doses for ^{90}Y-octreotide and ^{177}Lu-octreotate

	^{90}Y-octreotide		^{177}Lu-octreotate	
Organ	Mean (Gy/GBq)	13-GBq Course (Gy)	Mean (Gy/GBq)	29-GBq Course (Gy)
Kidney[a]	1.1–5.1	15–66	0.3–1.7	9–48
Bone marrow	0.02–0.2	0.3–2.6	0.01–0.08	0.3–2.3
Tumor	1.4–42	18–542	0.6–56	17–1624

Data derived from published studies[58] (with examples of standard full courses of therapy, using either 13 GBq or 29 GBq). In general, absorbed doses to normal organs (eg, kidney or bone marrow) are variable on an individual basis. Specific tumor-absorbed doses depend on the level of radioactivity concentration in individual lesions and increase with radioactivity accumulation in the tumor. Tumor doses themselves are also highly variable based on factors intrinsic to the tumor, particularly the density of somatostatin receptors on the tumor cell membranes, the dimension of the lesions, and the distribution of radioactivity within the lesions.

[a] Renal doses are calculated based on the use of renal protection with amino acid solutions.

^{90}Y-octreotide and 10% after ^{177}Lu-octreotate. Nevertheless, sporadic cases of myelodysplastic syndrome (MDS) or even overt acute leukemia have been reported.[14,38] Although predicted absorbed doses are lower than the conventional threshold for harm, both acute and permanent bone marrow toxicity is a cause for concern, particularly with repeated isotope administrations.[14,24,29,34] Dose-finding phase I studies indicate that the maximum cumulative administrable activity per cycle of ^{90}Y-octreotide, with renal protection, is 5.18 GBq.[28] An additional important observation derived from dosimetric studies is that hyperfractionation can lower the renal and bone marrow dose.[58,66] No dose finding studies have been conducted for ^{177}Lu-octreotate. Investigations using the dose-limiting toxicity method were abandoned, because literature data indicated that 7.4 GBq could be safely used as a maximum activity per cycle. Similarly, dosimetric studies indicated the advantage of hyperfractionation in lowering the renal and bone marrow dose.[34,44,58,66] In a phase I–II study treated with escalating activities of ^{177}Lu-octreotate up to 7.4 GBq/cycle in 51 patients, no major acute or delayed renal or hematological toxicity was observed and cumulative renal and bone marrow absorbed doses were within designated safety limits.[34] ^{177}Lu-octreotate demonstrated a higher tolerability compared with ^{90}Y-octreotide, largely due to the physical characteristics of the 2 radioisotopes.

An additional, although rare, consideration related to symptom exacerbation should be noted. A minority of individuals with functional lesions (eg, carcinoid, insulinoma, or Zollinger-Ellison syndrome) is susceptible. Paroxysmal amplification of symptoms is a consequence of massive radiation-induced cell lysis and subsequent release of bioactive amines or peptides into the bloodstream after PRRT. Such rare events can be rapidly managed by administration of cold somatostatin analogues, β-blockers, dextrose, or proton pump inhibitor agents dependent on the specific syndrome.[67,68]

FINAL CONSIDERATIONS

PRRT with either ^{90}Y-octreotide or ^{177}Lu-octreotate has been demonstrated to be efficient and relatively safe provided the known thresholds of absorbed and BED are carefully observed (Fig. 7). The renal and hematological toxicity profile is acceptable and can be further defined, if appropriate protective measures (such as amino acid protection and activity fractionation) are undertaken.

PRRT has also been demonstrated to induce a significant improvement in the QoL and diminution of symptoms related to the disease in most treated individuals. PRRT has a median PFS of more than 30 months, which represents a substantial improvement in comparison with many other therapeutic strategies used in NETs. In particular, individuals responsive to PRRT with tumor stabilization or reduction (~75% of the treated population) demonstrate a significant increase in survival (40–72 months from diagnosis). For these reasons, despite the absence of the results of randomized controlled trials, PRRT is considered one of the fundamentally effective therapeutic

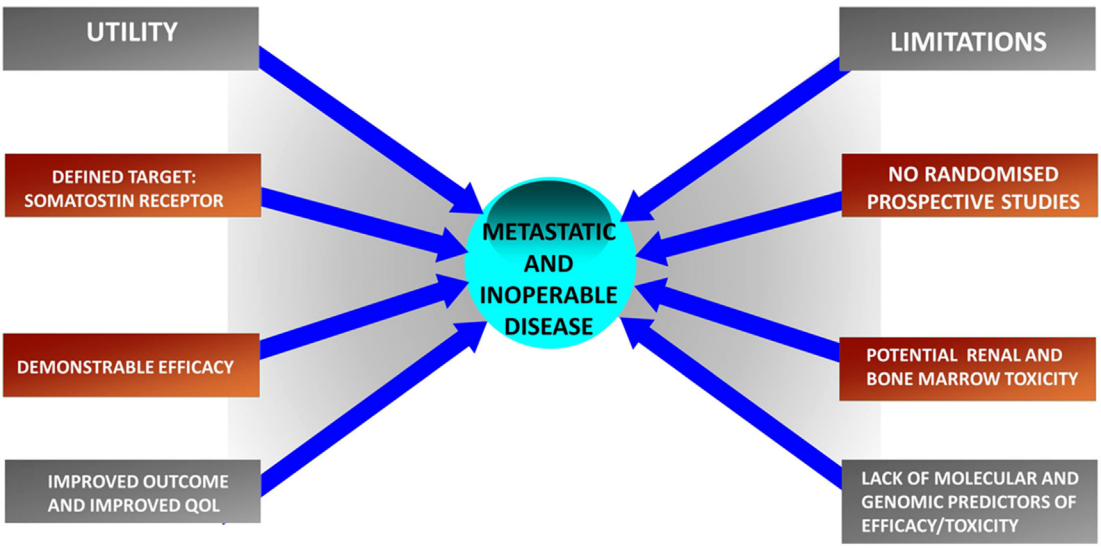

Fig. 7. Utility and limitations of PRRT in the treatment of NETs.

strategies in the management of NETs. As such, this modality of therapy (PRRT) has been included in the therapeutic algorithms proposed for NET disease management and has been accepted by the pertinent medical and scientific societies.[21,69–71] Despite such widespread acceptance and usage, there are several issues that require clarification in the near future. In particular, the precise timing of PRRT within the therapeutic algorithm of NETs requires delineation and reflects the relatively modest numbers of treated tumors, the relatively short follow-up, and the absence of randomized controlled trials. This critical limitation in defining the precise utility of PRRT will be addressed, at least in small bowel NETs, based on the outcome of a current ongoing multicenter study.

A further requirement in demarcation of the efficacy of PRRT is the need to more scientifically assess the parameters of response to the treatment. In particular, the specific molecular features of these tumors (indicators of radiation sensitivity), proliferative markers (Ki-67), and molecular indices defining response need delineation. Such information would further amplify the ability to assess efficacy beyond current parameters, such as evidence of disease extension, basal isotope uptake at receptor imaging, and morphologic assessment of the lesion type. Thus, pretreatment functional analysis of tumors using metabolomic parameters may convey information in regard to the likelihood of radiation sensitivity. Recent studies have noted that fluorodeoxyglucose (FDG) is a crucial parameter in predicting the duration of response to PRRT. Thus, individuals with positive FDG exhibit a significantly shorter PFS,[72] clear evidence that tumor glucose utilization represents a significant parameter in predicting therapeutic efficacy.

A further consideration is the assessment of the potential for renal and bone marrow toxicity. This area has not been rigorously investigated at a scientific level and remains a cause for concern among clinicians, given the potential for an effective therapy to engender a potentially critical series of adverse events. Radiation burden to tumor and normal organs is difficult to establish with acceptable accuracy, in the absence of the identification of individual factors that might redefine susceptibility. Alternatively, the use of treatment schedules with an excessively conservative approach, not considering the individual dosimetry and other biologic factors, may unreasonably limit the efficacy of treatment (see **Fig. 7**). In this regard, the delineation of molecular radiobiological parameters and individual, genetically based features inherent to predicting the efficacy and safety of radiopeptide therapy, would expedite the development of patient-specific and tumor-specific personalized therapy. The establishment of a profile of molecular determinants of both efficacy and toxicity would facilitate the use of the most efficient tumor irradiation and, at the same time, define the most conservative safety profile with respect to normal organs.

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