

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues

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Abstract

The purpose of this guideline is to assist physicians caring for patients with neuroendocrine neoplasia (NEN) in considering eligibility criteria for peptide receptor radionuclide therapy (PRRT) and in defining the minimum requirements for PRRT. It is not this guideline's aim to give recommendations on the use of specific radiolabeled somatostatin analogues for PRRT as different analogues are being used, and their availability is governed by varying international regulations. However, a recent randomized controlled trial, NETTER-1, has provided evidence that may establish ^{177}Lu -DOTA-octreotate (LutaThera®) as the first widely approved agent. It also makes recommendations on what minimal patient, tumour, and treatment outcome characteristics should be reported for PRRT to facilitate robust comparisons between studies.

Introduction and Background

Based on the frequent expression of somatostatin receptors (SSTR) in gastroenteropancreatic (GEP) neuroendocrine neoplasia (NEN) [1], especially in well-differentiated neuroendocrine tumour (NET) and demonstration of the ability to image this expression using radiolabeled peptides [2], it was a logical extension of the theranostic paradigms developed for thyroid cancer and other malignancies treated with radionuclides to also leverage SSTR expression as a therapeutic target. The use of high-administered activities of SSTR-binding ligands is now commonly known as peptide receptor radionuclide therapy (PRRT). In many parts of the world this use of radiolabeled somatostatin analogues is an established treatment modality for inoperable loco-regional or distant metastatic GEP-NET. It is also an emerging therapy in other countries in both the developing and developed world that have previously had limited access to this form of therapy. Over the past 2 decades several different radiolabeled somatostatin analogues have been applied. The

historical development of this therapy is discussed below. The majority of reported series using PRRT have come from single academic institutions. Industry-funded studies have been very limited and few multicentre trials have been performed. Comparison of outcomes between trials has been complicated by the varying criteria by which patients were selected for treatment, the differing treatment regimens used and the application of inconsistent outcome measures. Nevertheless, there is a long and relatively large clinical experience with PRRT and there has been a significant growth in clinical acceptance of this treatment modality throughout the world based on this experience.

Despite the variation in reported series, there is a relatively high degree of consistency in the reported response rates based on conventional morphologic imaging. Results of trials that have assessed response rates are tabulated by principal radionuclide in Table 1. These response rates, particularly those obtained using beta-emitting radionuclides, generally compare quite favourably with those obtained with chemotherapy and are generally substantially higher than those achieved with targeted agents, including everolimus and sunitinib, which have recently been approved in many countries based on the demonstration of a delay in disease progression compared to the control arm [3, 4]. However, the potential for selection bias in the patients entering trials of different forms of therapy must be recognised. Similarly, both progression-free survival (PFS) and overall survival (OS) data are very encouraging. Survival data from published studies are listed in Table 2. However, the lack of a control population for comparison has limited assessment of the significance and degree of benefit in comparison with other than historical controls. While it may be easy to criticise or lament the time that it has taken to perform rigorous prospective clinical trials using PRRT for this orphan disease, and particularly to perform randomised controlled trials, it needs to be recognised that most of these studies were performed without the financial backing of pharmaceutical companies or government sponsorship. Furthermore, they often involved compassionate use in patients who had exhausted all conventional forms of treatment and who may not have met eligibility criteria used for traditional pharmaceutical studies. Treating patients with advanced disease, who have failed other lines of therapy and have remained symptomatic or whose disease has continued to progress, is a staunch test of any therapy and the relatively high response rates and excellent disease control rates are particularly impressive in this patient population. Accordingly, there is a pressing need to define further where, within an integrated treatment pathway, this therapy should be instituted. Current guidelines place it as an option after other treatments have failed [5], which is appropriate in the context of current evidence and since it has been traditionally used as a salvage therapy. However, in the future, in certain situations PRRT may well be considered earlier in the treatment pathway.

The major focus of this guideline will be on the selection of patients for PRRT and discussion of the expected efficacy and side effects of ^{177}Lu -DOTA-octreotate since this is now the most widely available agent. Furthermore, this was the agent used in the NETTER-1 study, the only randomized controlled trial reported to date. Accordingly, this is the most likely agent to achieve regulatory approval and reimbursement in most jurisdictions in the near future. However, to put these recommendations in context, it is important to first understand the evolution of this therapy over the past two to three decades.

Early Studies with [^{111}In -DTPA 0 , Tyr 3] Octreotide

The first institutional trials of PRRT were performed during the 1990s using high cumulative activities of [^{111}In -DTPA 0 , Tyr 3]-octreotide in patients with metastatic neuroendocrine tumours [6, 7]. This is the same agent that is used for diagnostic imaging and is marketed as OctreoScan®. Early reports were encouraging [8-10] but also provided the first evidence of the potential for myelodysplastic syndrome (MDS) and leukaemia [8]. This occurred in 3 of six patients treated with very high cumulative activity. Although these series reported favourable effects on symptomatology, CT-assessed tumour regression was only rarely observed. This is not surprising given the short particle range of the Auger electrons of ^{111}In and consequent lack of crossfire effects. In an attempt to increase the effectiveness of this therapy, radiosensitizing chemotherapy was added to this protocol with apparent enhancement in symptomatic and scintigraphic responses [11]. The cost and limited response rates of this therapy have, however, limited its ongoing use.

Early Studies with [^{90}Y -DOTA 0 , Tyr 3] Octreotide

Another radiolabeled somatostatin analogue that was developed for PRRT is [^{90}Y -DOTA 0 , Tyr 3] octreotide (^{90}Y -DOTA-TOC; OctreoTher). Phase-1 and phase-2 PRRT trials with this agent [12-14] demonstrated improved rates of tumour regression but severe renal toxicity was also noted in some patients to whom renoprotective amino acids were not administered. Nevertheless, other studies using amino acid infusion demonstrated less nephrotoxicity [15-17]. Despite differences in the protocols applied, objective response rates in most of the studies with [^{90}Y -DOTA 0 , Tyr 3] octreotide were between 10 and 30%, and were therefore substantially better than those obtained with [^{111}In -DTPA 0 , Tyr 3] octreotide. Similar early studies [18] encouraged a large international study of OctreoTher, which was performed in the early 2000s but only formally reported many years later [19]. These reports and the largest single centre study reported by the Basel group [20] established the effectiveness of this therapy but also confirmed concerns about its potential nephrotoxicity. Because the path length of beta particles from ^{90}Y is around 10mm, re-uptake of peptides in the proximal convoluted tubules of the kidneys brings a greater percentage of glomeruli within range of particulate irradiation compared to ^{177}Lu with its beta particle length of 1-2mm. This combined with a short physical half-life may account for the higher apparent risk of renal impairment

observed with ^{90}Y than with ^{177}Lu (see below). A recent study, evaluated outcomes of 56 patients treated with [^{177}Lu -DOTA⁰, Tyr³] octreotide, which is the same peptide used with ^{90}Y [21]. There were no serious adverse events reported and, in particular, no nephrotoxicity was observed, supporting the importance of the radionuclide for this outcome.

Studies with [^{177}Lu -DOTA⁰, Tyr³] Octreotate

The somatostatin analogue [DOTA⁰, Tyr³] octreotate differs from [DOTA⁰, Tyr³] octreotide only in that the C-terminal threoninol is replaced with threonine. However, Reubi *et al.* [22] reported a nine-fold increase in its affinity for the SSTR subtype 2. This higher affinity was also supported by findings of clinical studies [23, 24]. Assessment of toxicity in a group of 504 patients treated up to an intended cumulative activity of 27.8–29.6 GBq (750–800mCi), usually given as 4 cycles of treatment at 6–10 weekly intervals, revealed that, in the first 24 hours the most common symptoms were nausea (25%), vomiting (10%), and pain (10%) [25]. In a subset of patients reported separately [26], 6 of 479 (1%) patients with very hormonally active neuroendocrine tumours had a clinical crisis after administration due to massive release of bioactive substances. Although all these patients recovered with supportive care, this emphasises the importance of careful selection, preparation and monitoring of patients receiving PRRT (Table 3).

In the larger group, involving 510 patients [25], haematological side effects (CTCAE grade 3 or 4) occurred after 3.6% of individual administrations but in 9.5% of patients receiving multiple cycles. Mild, reversible alopecia was reported by 62% of patients. More serious, delayed side effects occurred in 9 patients, including reduced kidney function in 2 patients, liver toxicity in 3 patients and MDS in 4 patients, although other disease-related factors may have been involved in some of these adverse outcomes. A recent summary of toxicity data in 807 patients receiving PRRT with ^{177}Lu , ^{90}Y or regimens of both radionuclides, confirmed the lower toxicity profile of ^{177}Lu compared to ^{90}Y analogues [27]. Long-term follow-up by other groups has similarly demonstrated low rates of nephrotoxicity [28–30]. Effects of PRRT using this agent on endocrine function have been reported in a small study involving 79 patients, including 35 men and 21 post-menopausal women with a follow-up period of 1–2 years [31]. Although small measurable changes were seen, these were not generally clinically significant and the authors' conclusion was that PRRT should be regarded as a safe treatment modality with respect to short- and long-term endocrine function.

In a large single institutional report of efficacy with this agent, tumour response was evaluated in 310 patients with GEP-NET [25]. Complete response (CR) was found in 5 (2%) patients, partial response (PR) in 86 (28%), minimal response (MR) in 51 (16%), stable disease (SD) in 107 (35%), and progressive disease (PD) in 61 (20%). Higher remission rates were positively correlated with high uptake during pre-therapy OctreoScan and a limited number of liver metastases. These data suggest that the intensity of uptake and

burden of disease on diagnostic scans are predictors of radiation dose delivery to disease and may thereby influence the likelihood of response.

Median time to progression was 40 months from start of treatment in the 249 patients who either had SD or tumour regression (MR, PR and CR) but these data excluded the 20% patients who progressed on treatment. Median overall survival was 46 months from start of therapy. Comparing similar patient subgroups from different interventional and observational studies, there seemed to be a survival benefit of 3.5–6 years. Importantly, since these therapies seldom lead to durable complete remissions and must therefore be considered palliative, quality of life has been shown to significantly improve following [$^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$] octreotate PRRT [32]. A more recent study reporting outcomes from a prospective German registry reported outcomes in 450 patients treated at 5 different centres, primarily with [$^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$] octreotate but including some patients receiving either a combination of Lutetium-177 and Yttrium-90 agents or the latter alone [33]. PRRT was administered according to prior guidelines [34]. For the entire population the progression-free survival was 41 months and the overall survival was 59 months. In the 76 (17%) patients receiving [$^{90}\text{Y-DOTA}^0, \text{Tyr}^3$] octreotide both progression-free and overall survival were decreased compared to patients receiving Lutetium-177 alone or in combination with Yttrium-90 agents. However, caution is required since the criteria by which patients were chosen for a particular therapy were not described. Response by RECIST 1.1 criteria were available in 357 (79%) patients with 7% CR, 28% PR, 59% SD and 5% PD. Considering that patients were required to have progressive disease prior to treatment, the disease control rate was thus 95%. As with other studies, severe adverse events were uncommon with grade 3 leukopaenia and thrombocytopaenia in 1.1% and 1.3% of patients, respectively, and only a single episode of grade 4 thrombocytopaenia. There was only a single case of grade 3 and no grade 4 renal toxicity. No cases of MDS or leukaemia were reported although median follow-up was only 24.4 months, which may be too short to capture this relatively late adverse outcome. Two relatively recent studies from the Bonn group emphasize that differential response rates occur in NET of differing primary origin. Although both studies included only patients with stage IV, WHO G1/2 NET, the response rate was substantially higher in pancreatic NET [35] than in small intestinal NET [36] even though overall survival rates were similar in both series. It is also important to note that the NETTER-1 study described below only applied to mid-gut NET, including the jejunum, ileum, appendix and right colon, for which there are currently limited approved targeted therapies. Nevertheless, retrospective analyses of outcome in pancreatic NET suggest similarly impressive survival [35, 37]. The neoadjuvant use of PRRT in patients with unresectable or borderline resectable primary pancreatic tumours has also been suggested [38, 39].

NETTER-1: The First Randomised Control Trial of PRRT

The first results of the only reported randomized trial concerning the efficacy of PRRT have recently been reported [40]. The NETTER-1 trial involved a 1:1 randomisation of 229 patients with progressive metastatic small intestinal NET on 30mg monthly of Sandostatin LAR to either ^{177}Lu -DOTA-octreotate with continuing Sandostatin LAR at 30mg per month or to dose escalation of Sandostatin LAR to 60mg monthly. The PRRT protocol involved 4 cycles of 7.4GBq (200mCi) of ^{177}Lu -DOTA-octreotate at 8 weekly intervals. Most (77%) patients received all planned cycles of treatment. For the PRRT arm, a median PFS was not reached compared 8.4 months ($p < 0.001$) for dose escalated Sandostatin LAR. All predefined sub-analysis groups had improved PFS with ^{177}Lu -DOTA-octreotate compared to controls. Although the relatively short duration of follow-up at the time of publication limited assessment of OS in either group, interim analysis indicated that the estimated risk of death was 60% lower in the ^{177}Lu -DOTA-octreotate group than in the control group (hazard ratio 0.40; $P = 0.004$). The objective response rate was 18% versus 3% ($p < 0.0004$). Grade 3 or 4 neutropenia, thrombocytopenia and lymphopenia occurred in 1%, 2% and 9% of patients in the PRRT arm versus none in controls. One case of myelodysplastic syndrome was attributed to PRRT.

The most commonly reported acute side-effects of PRRT were nausea and vomiting. These occurred primarily during amino acid infusion given for renal protection and resolved with cessation of the infusion. In this trial, commercial amino acid solutions (Aminosyn II 10% [21.0 g of lysine and 20.4 g of arginine in 2L of solution] or VAMIN-18 [18 g of lysine and 22.6 g of arginine in 2L of solution]) were administered. These solutions are more concentrated than those used in most institutional trials, which typically include only lysine and arginine. Use of anti-emetic medication was not reported but is an effective means to reduce these side-effects.

Although these results are entirely in keeping with other phase I-II institutional trials and retrospective analyses of single institutional experience, final analysis of the longer-term toxicity, quality of life and patient outcome data are not yet available through peer-reviewed publication.

Studies Combining Radionuclides and Utilising Radiosensitising Chemotherapy

The above trials and other institutional series detailed in Table 1 suggest that treatment with radiolabeled somatostatin analogues is a promising therapeutic modality in the management of patients with inoperable or metastasized neuroendocrine tumours. However, there remains significant variability in the approach to delivering this therapy. While the NETTER-1 trial used a fixed administered activity of ^{177}Lu -DOTA-octreotate, others have used variable administered activities, different radionuclides, routes of administration and intervals between treatments. Eligibility criteria have also varied.

A variation in treatment protocol has included the use of combinations of different radionuclides to optimize delivery to lesions of different sizes. For example, ^{90}Y has theoretical advantages for larger lesions with more heterogeneous uptake due to its long beta particle path length whereas ^{177}Lu is better suited to smaller lesions [41]. Accordingly, using these isotopes in combination might provide better radiation dose delivery across the range of lesion sizes that is often present in individual patients. Indeed, results of combination therapies are encouraging [42, 43]. Similarly, although most PRRT has involved intravenous administration, liver dominant disease may benefit from hepatic arterial administration [44, 45] but no prospective comparison studies are currently available.

While a standardised approach is likely to meet better the regulatory requirements for reimbursement, the need for a more individualised approach has also been argued [46]. This includes the potential use of PRRT in combination with other therapies in a manner analogous to chemoradiation, which is now widely used in treatment of various solid tumours.

Studies combining PRRT with radiosensitizing chemotherapy, which has been called peptide receptor chemoradionuclide therapy (PRCRT), have shown that this is feasible with minimal incremental toxicity. This approach has included studies with infusion of 5-fluorouracil or administration of its oral pro-drug, capecitabine [47-51] and a further study using capecitabine and temozolamide [52]. A randomized controlled trial of the latter combination is currently underway in Australia whereas the former is being tested in the Netherlands. While apparently safe and efficacious there are currently no data confirming whether PRCRT is superior to PRRT and therefore current guidelines refer to patients being considered for PRRT. The rationale for combining chemotherapy with PRRT is strongest for higher grade NEN. In lower grade neuroendocrine tumours, which would be expected to have longer survival independent of therapeutic effects, the potential benefits of chemotherapy need to be balanced against the risks of inducing myelodysplastic syndrome (MDS) or leukaemia, which may be more likely when an alkylating agent like temozolamide is used [53]. A recent report from France, where alkylating agents are widely used in chemotherapy regimens, indicated that 20% of patients receiving PRRT as a salvage therapy developed MDS [54] but these data have been disputed by a more comprehensive review of the experience with PRRT from multiple international trial and reported case series [55]. The overall risks of MDS and leukaemia appear to be low (<2%) with PRRT, as described in a recent comprehensive review of the literature [56]. Accordingly, a small increase in the risk of MDS by combining PRRT with an alkylating agent like temozolamide could be best justified in patients with a poor prognosis and a high likelihood of disease progression. The presence of increased glycolytic activity of ^{18}F -fluoro-deoxyglucose (FDG) tends to increase with tumour grade and has been shown to predict for poor survival in NEN [57, 58]. Indeed, it may be a more

powerful prognostic marker than conventional measures including the percentage of cells staining for Ki-67, a proliferation marker [59]. In patients who retain SSTR expression but are FDG-avid, encouraging response rates and survival rates have been reported with PRCRT [51, 60]. An ongoing randomised control trial in Australia is comparing PRCRT with CAPTEM (capecitabine plus temozolomide) with CAPTEM or PRRT depending on the primary site of origin.

Recommendations to Improve Comparability Trials of PRRT

A major limitation posed in comparing the currently published trials is a lack of consistency in design and analysis of outcomes. To address these issues, it is important to recognise the heterogeneity that exists in the biology and, hence, outcomes of different types, primary sites of origin, and grades of tumour within the spectrum of neuroendocrine neoplasia. For very low-grade tumours, progression of even widely metastatic disease can be minimal over many years. As such, therapeutic interventions are relatively unlikely to significantly impact survival and measures such as PFS and OS are probably inappropriate end-points. Furthermore, slowly dividing tumours are often highly resistant to radiation and objective response rates would therefore be expected to be low. Consequently, the rationale for treating such patients with PRRT, with its attendant cost and risks, needs to be critically balanced against observational or treatment regimens aimed at symptomatic control. In patients with uncontrolled symptoms related to hormonal secretion or direct mechanical effects of tumour, e.g. local pain, but without documented progression, amelioration or abrogation of symptoms and measures of quality-of-life are much more relevant end-points by which to assess the utility of PRRT than are measures of survival or morphological response. Conversely, with intermediate-grade tumours, morphological progression poses risk to the function or integrity of involved organs as well as potentially exacerbating hormonal syndromes in functional tumours. In such cases, disease control rates and PFS rates are more important measures of treatment benefit but quality-of-life measures are also important. In high-grade tumours, OS becomes highly relevant since without disease control, death can rapidly ensue. Accordingly, trials must have clear specification of either the range of grades of tumour that were included (preferably using pathological criteria detailed in the updated ENETS guidelines [61]) or else a definition of the period over which progression was observed and the method by which progression was established. To elucidate the role in tumours arising in different sites, heterogeneity within trials should be defined by careful definition of the site of origin. Multi-institutional trials may be necessary to further define the role of PRRT in rarer forms of metastatic NET such as insulinoma, glucagonoma, VIPoma and somatostatinoma. Given the importance of SSTR expression to the efficacy of PRRT, the type of imaging performed in selecting patients should be stated. Given the technical differences between planar and SPECT/CT imaging of ^{111}In -octreotide in terms of contrast resolution and lesion

localisation and, even more so, between conventional nuclear medicine imaging and ^{68}Ga -based PET/CT studies, the degree of SSTR-expression may not be comparable for studies requiring a “positive” scan for eligibility. It is, however, important that, whatever molecular imaging technique is used to select patients for treatment, the same methodology should also be utilised to assess response. Furthermore, using a more sensitive scanning technique may erroneously suggest progression and therefore should not be used as the sole criterion for instituting treatment in otherwise stable patients unless treatment is indicated for symptomatic control. A more detailed discussion of the use of diagnostic techniques in staging and therapeutic monitoring of patients with NEN is detailed in the recently revised consensus imaging guidelines [62]. How lesions that are identified on structural imaging but which have low or absent apparent SSTR-expression are handled should also be documented. If FDG PET/CT or biopsy is not performed to characterise such lesions there is a possibility that dedifferentiated disease might be overlooked. Because lesions that lack sufficient SSTR expression for visualisation on diagnostic imaging are likely to receive minimal radiation and yet probably represent the major prognostic determinant of outcome, inclusion of patients with such lesions may lead to underestimation of the efficacy of PRRT compared to that in patients in whom all disease sites have high target expression. With ^{68}Ga -DOTA-octreotate (NETSPOT®) being recently approved by Federal Drug agency in the United States and ^{68}Ga -DOTA-octreotide approved by the European Medicines Agency, high-quality SSTR-imaging will become more widely available and should become the standard of care in clinical trials. FDG PET/CT is also encouraged with comparison of the spatial distribution of each tracer when both are expressed [63].

While most groups have applied standard response criteria based on morphological imaging with CT or MRI, PRRT also lends itself to more sophisticated measures of response. These include the combination of serum biomarkers and functional imaging. While the oncology community and regulators have become habituated to tumour shrinkage or growth as indicators of response, we know that many lesions identified on functional imaging are overlooked or not detectable on anatomical imaging [64]. Accordingly, detection of new lesions as an indicator of progression or disappearance of prior lesions may be more sensitively detected by SSTR-imaging than by CT. While morphologic regression is clearly desirable, more patients can be demonstrated to have responded by reduction in the extent or number of lesions on SSTR imaging and the prognostic value of such response is similar [50]. The availability of serum biomarkers like chromogranin-A (Cg-A) or other specific hormones also provides an important means to assess response. Since Cg-A is not routinely elevated in all cases of metastatic NEN and can also be elevated in a range of other situations, including deterioration in cardiac or renal function, both of which can be complications of the underlying disease or its treatment [65], there is a need for improved

biomarkers of response. The use of functional imaging and biomarkers to assess response to radionuclide therapy has a precedent in thyroid cancer wherein radioiodine scanning and thyroglobulin measurement have long been considered the optimal means to assess the efficacy of ^{131}I therapy of metastatic thyroid cancer. Because the timetable and type of response assessment can impact the apparent progression-free survival of patients, follow-up strategies should be formalised and reported.

In patients treated for symptomatic disease rather than disease progression, symptomatic control rates and use of standard quality-of-life instruments are to be encouraged and the timing and durability of symptom control should also be reported.

PRRT Requirements

Regulatory Aspects

Permission to perform PRRT should be obtained according to local and national regulations. When there is no overarching approval for this therapy locally, Ethics Committee approval should be obtained and eligible patients should sign an informed consent form that acknowledges the known risks of this therapy, including particularly the potential for nephrotoxicity, reversible haematological toxicity and the low but important long-term complication of MDS or leukaemia. The production of the peptide should also meet local regulatory conditions, which may include meeting GMP criteria. Storage and dispensing should also be according to national legislation.

Eligibility Criteria

Eligibility and clinical decision-making should be based on multidisciplinary discussion. Where treatment has a clear intent to palliate uncontrolled symptoms, contra-indications may be waived. The most important inclusion criteria are listed in Table 4. Although most reports have focussed on patients with lower grade NET (ENETS G1-2), provided SSTR-expression is adequate, there is emerging evidence that this therapy may be effective in patients with higher-grade G2 NET and G3 NEC who have failed a trial of chemotherapy or who are deemed unsuitable for this therapy. In particular, a recent study confined to patients with FDG-avid disease demonstrated similar response rates to those in other studies and encouraging progression-free [51] and overall survival [60]. FDG-avidity has been shown to increase with increasing tumour grade and to be associated with an adverse prognosis with conventional therapy [57-59]. The role of FDG PET/CT in selecting patients for PRRT is further discussed in the imaging guidelines [62]. The concept of spatial concordance between lesions identified on SSTR-imaging and those expressing the glycolytic phenotype in selecting patients for PRRT [66] is a fundamental principle underpinning the theranostic paradigm [67]. There is increasing recognition that the degree of differentiation on histopathological examination varies within the group of tumours with a Ki-67 >20%, i.e. G3 NEN, and that this impacts prognosis [68, 69]. A new classification of well-differentiated G3

NET is likely to be included in the revised World Health Organisation grading system of NEN. As a feature of differentiation, SSTR expression may be complementary to pathology in differentiating well- from poorly-differentiated G3 NEN. Recent evidence suggests SSTR PET imaging results are highly correlated with SSTR-2 expression on immunohistochemistry but more accurate for predicting individual prognosis [70].

Contraindications

All contraindications must be considered in the context of the other therapeutic options available, the patient's life-expectancy and whether the intent of treatment is symptom palliation or oncological control. Most are relative rather than absolute contraindications. Those that are generally considered absolute contraindications are marked by an asterisk.

- Significant sites of active disease as determined by unequivocal, contrast-enhancing lesions on CT or MRI that lack SSTR expression, which can be confirmed by ^{18}F -fluorodeoxyglucose PET/CT if available (Use of concomitant chemotherapy may be an option in such cases)
- Pregnancy or ongoing lactation*
- Moderate to severe renal impairment (i.e. creatinine clearance $<50\text{ml/min}$) (Patients on dialysis can be treated with a significantly reduced administered activity to account for lack of urinary excretion with dialysis delayed for 24 hours after treatment subject to consultation with the managing nephrology team)
- Impaired haematological function, i.e. Hb $<5\text{mmol/L}$ (8g/dl); platelets $<75 \times 10^9/\text{L}$; WBC $<2 \times 10^9/\text{L}$
- Severe hepatic impairment, i.e. total bilirubin $>3\text{x}$ upper limit of normal or both an albumin $<25\text{g/L}$ and pro-thrombin time increased >1.5 ULN, indicating biosynthetic liver failure*
- Severe cardiac impairment (New York Heart Association grade III or IV) *
- Moderate to severe right heart valvular disease (Valve replacement is strongly encouraged prior to PRRT in such cases, please refer to guidelines for management of carcinoid heart disease)
- Inability to comprehend and consent for PRRT due to a psychiatric or other neurological disorder (e.g. dementia) without the support of a designated health advocate or legal guardian*

Laboratory Evaluations Required before Each Therapy Cycle

- Haematology; Hb, WBC plus differential, platelet number
- Kidney function; creatinine and urea with formal creatinine clearance if abnormal
- Liver function; bilirubin, albumin, ALP, GGT, ALT, AST, INR
- Electrolytes; serum potassium and corrected serum calcium
- LDH

- Chromogranin-A and other secretory products including specific hormones, if elevated at baseline

Patient Preparation and Monitoring during PRRT

When clinically feasible, the most recent long-acting somatostatin analogue administration should be 4-6 weeks before PRRT [34]. If necessary for symptom control, patients can continue supplementary short-acting formulations up to 8 hours before PRRT. For symptomatic control, patients on long-acting formulations may co-administer short-acting formulations in the first 7–10 days after their long-acting formulation has been restarted if required.

Infusion of amino-acid solutions that contain lysine and arginine is essential to reduce kidney radiation-absorbed dose when performing PRRT [71]. The duration of infusion recommended has varied from as low as 2-3 hours in patients with normal renal function [29] to up to 10 hours [34, 72]. However, the most commonly used regimen is that developed by the Erasmus Medical Center, which recommends 25g lysine and 25g arginine in 1 litre saline infused over 4 hours, starting 30min before the administration of the radiopharmaceutical. Alternatively, other commercially available amino acid solutions can be used [73]. The infusion of amino acids can be associated with hypokalaemia so it may be prudent to correct these if low prior to treatment [74]. A detailed discussion of the mechanism of renal protection and the extensive research that underpins the use of amino acids is beyond the scope of this review. Due to the variability in availability and composition of amino acid solutions, infusion protocols may need to be adapted according to local availability. Use of 5-HT₃-antagonists, such as granisetron as a premedication is recommended to reduce nausea and vomiting, which are prominent symptoms when commercial amino acid solution are used, as they were in NETTER-1 [75].

For PRRT with ⁹⁰Y-labelled analogues, it is possible to do 'Bremsstrahlung' scintigraphy of the whole body and to perform SPECT images using this technique after therapeutic administration. Although primarily used to evaluate radiation dose from ⁹⁰Y-microsphere therapy [76], it is also possible to assess dose delivered by doing post-treatment PET/CT [77]. While not widely available, it is also possible to perform prospective dosimetry by using PET/CT using ⁸⁶Y-labelled ligands [78] or by extrapolating from co-administered ¹¹¹In-DTPA-octreotide [79]. When using ¹⁷⁷Lu-labelled analogues, individual dosimetry based on post-therapy planar scans and, if feasible, blood and urine collections, is the most widely used method but techniques for quantitative SPECT/CT have been developed [80, 81] and are now being provided by various vendors.

Written instructions should be given to patients regarding travel and contact with others after the therapy, according to national/international regulations.

Blood cell counts should preferably be performed 2, 4 and 6 weeks after each therapy cycle. If radiosensitizing chemotherapy is used, additional assessment of blood counts at 1 week is recommended. In case of CTCAE toxicity grade 3 or 4, testing should be repeated every week until recovery is documented. If indicated clinically, blood product support should be performed according to national guidelines.

Quality of life assessments at regular intervals are recommended.

Treatment Scheme

There are no randomized clinical trials available comparing optimal administered activity per treatment cycle, optimal cycle interval, or optimal cumulative administered activity for either ^{90}Y -labelled or for ^{177}Lu -labelled somatostatin analogues. Therefore, no strict guidelines can be provided. The Basel group have used a weight-based administration for ^{90}Y ($3.7\text{GBq}/\text{m}^2$ body surface area) with up to 10 cycles administered [20]. The NETTER-1 trial used up to 4 cycles of a fixed administered activity of 7.4 GBq (200mCi) per cycle, which is based on the protocol developed at the Erasmus Medical Center [82]. Variation from this administered activity based on tumour burden, extent of bone marrow involvement, renal function and body habitus may be appropriate but must depend on local expertise and clinical judgment [46]. The potential role of prospective radiation dosimetry requires further clarification. Similarly, combination of different radionuclide therapy combinations based on lesion size and distribution will require further validation. Although there are theoretical advantages in combining ^{90}Y and ^{177}Lu with respect to delivering improved radiation delivery to larger and smaller deposits respectively [83] and with different routes of administration, as discussed above, these cannot yet be recommended as routine approaches. Nevertheless, there are data supporting this approach with a prospective trial demonstrating improved survival in patients receiving a tandem treatment of both agents compared to patients receiving only ^{90}Y -based PRRT [84]. More recent data using ^{90}Y -DOTA-octreotate followed by ^{177}Lu -DOTA-octreotate for patients with bulky disease demonstrated relatively high response rates and survival [85]. In the large series of patients treated at Basel, the median survival of the subgroup of patients receiving both ^{90}Y and ^{177}Lu -DOTA-octreotide was more than 5 years [42].

Discontinuation of Treatment

Progressive disease during the treatment period, based either on imaging studies or on the patient's clinical condition, is possibly a reason to discontinue the treatment. However, it is important to recognize the possibility of a flare in symptoms due to release of preformed hormones or a rise in serum tumour markers due to cell death or damage, most evident with the first cycle [26]. There is also a possibility of pseudo-progression on morphologic imaging. If this is suspected, confirmation of progression by functional imaging is recommended, particularly if hepatic density changes are apparent on non-contrast CT or there is variation

in the imaging technique with respect to timing of intra-venous contrast. For example, the resolution of fatty liver that can accompany abrogation of hormonal effects of functional pancreatic NET can make lesions appear more conspicuous on non-contrast CT and therefore simulate progression. Similarly, development of cystic necrosis or development of sclerosis at sites of previously occult bone metastases can also simulate progression. In these scenarios, improvement in molecular imaging appearances of the lesions in question or the regression or stability on serial conventional imaging can allow ongoing therapy. Prolonged (i.e. more than 2–3 months) CTCAE grade 3 or 4 haematological, renal, or hepatic toxicity may be a reason to modify the cycle dose or to discontinue treatment, according to local protocols. National Cancer Institute Common Terminology Criteria are recommended for reporting adverse events in clinical trials.

Follow-Up Monitoring

Please refer to the guidelines regarding follow-up of patients [86]. However, as progression-free survival is increasingly used as a measure of therapeutic efficacy in comparing therapies, the method and timing of follow-up imaging should ideally be harmonized. Assessment by a combination of anatomical imaging, molecular imaging and biomarker analysis at 3 and 12 months following completion of a course of PRRT could provide appropriate benchmarks for G1 NET but more frequent assessment is recommended for patients with G2 and G3 tumours. The tempo of progression prior to treatment should also guide the frequency of follow-up evaluation. For patients with higher grade or FDG-avid disease, evaluation every 3 months may be appropriate until there is clear evidence of disease control.

Conclusion

PRRT, irrespective of the radionuclide or peptide used, appears to be a highly effective therapy. Toxicity profiles are modest but can rarely include life-threatening events of which clinicians and their patients must be aware and remain vigilant to mitigate by careful selection, preparation and follow-up. These recommendations should not be considered prescriptive but rather need to be adapted to the circumstances of individual patients and to local experience and conditions.

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Table 1. Tumor responses in patients with GEPNETs, treated with different radiolabeled somatostatin analogues

Center (ref.)	Studies using PRRT	Ligand	Patient, n	Tumor Response					
				CR	PR	MR	SD	PD	CR+PR
Rotterdam	Valkema et al. 2002 [8]	[¹¹¹ In-DTPA ⁰]octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0%
New Orleans	Anthony et al. 2002 [9]	[¹¹¹ In-DTPA ⁰]octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8%
Milan	Bodei et al. 2003 [17]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29%
Basel	Waldherr et al. 2001 [13]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24%
Basel	Waldherr et al. 2002 [14]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33%
Multicenter	Valkema et al. 2006 [87]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)	9%
Multicenter	Bushnell 2010 [19]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	90	0	4 (4%)	NA	63 (70%)	11 (12%)	4%
Copenhagen	Pfeifer 2011 [88]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	53	2 (4%)	10 (19%)	NA	34 (64%)	7 (13%)	23%
Warsaw	Cwikla 2010 [89]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotate	58	0	13 (23%)	NA	44 (73%)	3 (5%)	23%
Warsaw	Kunikowska et al. 2011 [84]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotate	25	0	5 (20%)	NA	13 (52%)	7 (28%)	20%
Rotterdam	Kwekkeboom et al. 2008 [25]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29%
Gothenburg	Sward et al. 2010 [90]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	26	0	6 (38%)	NA	8 (50%)	2 (13%)	38%
Lund	Garkavij et al. 2010 [91]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	12	0	2 (17%)	3 (25%)	5 (40%)	2 (17%)	17%
Milan	Bodei et al. 2011 [92]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	42	1 (2%)	12 (29%)	9 (21%)	11 (26%)	9 (21%)	31%
Bonn	Ezziddin et al. 2014 [35]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate [§]	68	0	41 (60%)	8 (12%)	9 (13%)	10 (15%)	60%
Bonn	Sabet et al. 2015 [36]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate ^{§§}	61	0	8 (13%)	19 (31%)	29 (47.5%)	5 (8.2%)	13%
Meldola	Sansovini et al. 2013 [37]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate [§]	26 [^]	3 (12%)	7 (27%)	NA	12 (46%)	4 (15%)	30%
Meldola	Paganelli et al. 2014 [93]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate ^{§§}	25 [^]	1 (4%)	0	NA	20 (80%)	4 (16%)	4%
Bad Berka	Baum et al. 2016 [21]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotide	43	9 (20.9%)	10 (23.3%)	NA	12 (27.9%)	12 (27.9%)	41%
Multicentre	Strosberg et al. 2017 [40]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotide	101	1 (1%)	17 (17%)	NA	NA	NA	18%
<i>Studies using PRCRT</i>									
Fremantle	Claringbold et al. 2011 [49]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	33	0	8(24%)	NA	23 (70%)	2 (6%)	24%
Melbourne	Kong et al. 2014 [50]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	58 [§]	0	17 (30%)	5 (9%)	16 (29%)	18 (32%)	30%
Melbourne	Kashyap et al. 2015 [51]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate [*]	40	1 (2%)	11 (28%)	NA	27 (68%)	1 (2%)	30%
<i>Studies using a combination of [⁹⁰Y-DOTA⁰,Tyr³]octreotate and [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate</i>									
Warsaw	Kunikowska et al. 2011 [84]	Tandem	25	0	3 (12%)	NA	16 (54%)	8 (32%)	12%
Melbourne	Kong et al. 2016 [94]	Sequential ^{**}	19	0	8 (42%)	4 (21%)	7 (37%)	0	42%

PRCRT, peptide receptor chemoradionuclide therapy; Tandem, Co-administration of both radionuclides; Sequential, Use of ⁹⁰Y-PRRT followed by ¹⁷⁷Lu-PRRT for subsequent cycles. [^] Full Dosage group (26 GBq). [§] Response assessment limited to patients with progression within 12 months of study entry. ^{*} Included only patients with at least one site of FDG-avid disease. ^{**} All patients required at least one lesion >4 cm in diameter. [§] Included only patients with G1/2 pancreatic NET. ^{§§} Included only patients with G1/2 small intestinal NET.

Table 2. Survival data in patients with GEPNETs, treated with different radiolabeled somatostatin analogues

Center (ref.)	Ligand	Patient, <i>n</i>	PFS	OS	
Multicenter	Valkema et al. 2006 [87]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	58	29	37
Multicenter	Bushnell 2010 [19]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	90	16	27
Copenhagen	Pfeifer 2011 [88]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	53	29	
Warsaw	Cwikla 2010 [89]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotate	58	17	22
Basel	Villard et al. 2012 [42]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotide	237	NA	47.5
Warsaw	Kunikowska et al. 2011 [84]	[⁹⁰ Y-DOTA ⁰ ,Tyr ³]octreotate	25	NA	26.2
Rotterdam	Kwekkeboom et al. 2008 [25]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	310	33	46
Milan	Bodei et al. 2011 [92]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	42	NA	>36
Meldola	Sansovini et al. 2013 [77]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate [§]	1026	>30	>30
Meldola	Paganelli et al. 2014 [78]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate ^{§§}	25	36	>60
Bonn	Ezziddin et al. 2014 [35]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate [§]	68	34	53
Bonn	Sabet et al. 2015 [36]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate ^{§§}	61	33	61
Melbourne	Kong et al. 2014 [50]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	68	NA	>60
Melbourne	Kashyap et al. 2014 [51]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate*	640	48	55*
Bad Berka	Baum et al. 2016 [21]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotide	143	30.3	34.7
Multicentre	Strosberg et al. 2017 [40]	[¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotide	101	>20	NA
Warsaw	Kunikowska et al. 2011 [84]	[⁹⁰ Y+ ¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate	25	NA	>34.6
Basel	Villard et al. 2012 [42]	[⁹⁰ Y+ ¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotide	249	NA	66.1
Melbourne	Kong et al. 2016 [94]	[⁹⁰ Y+ ¹⁷⁷ Lu-DOTA ⁰ ,Tyr ³]octreotate**	26	33	>35

* Overall survival updated in [60]. ** Sequential use in patients with at least 1 lesion >4 cm. § ●●●●. §§ ●●●●.

Table 3

PRRT: Acute and Subacute Side-Effects
<ul style="list-style-type: none"> • Nausea after 25% of administrations* • Vomiting after 10% of administrations* • (Abdominal) Pain after 10% of administrations • Temporary mild / G1 Hairloss in 60% of patients after [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate • Grade 3/4 Hematological Toxicity in <15% of patients • Hormonal Crises in <1% of patients

* may be reduced by appropriate pre-medication.

Table 4

PRRT: Inclusion Criteria
<ul style="list-style-type: none"> • Inoperable/metastatic well-differentiated (G1/G2) NET • Well-differentiated G3 NET may be considered (further data are required on response rates and survival in this newly-defined subgroup) • Sufficient tumour uptake on the diagnostic somatostatin receptor scintigraphy • Sufficient bone marrow reserves (grade 1-2 haematological toxicity usually accepted) • Creatinine clearance > 50 ml/min • Karnofsky Performance Status >50 • Expected survival > 3 months • Signed Informed Consent

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