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GUIDELINES

The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

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Abstract Peptide receptor radionuclide therapy (PRRNT) is a molecularly targeted radiation therapy involving the systemic administration of a radiolabelled peptide designed to target with high affinity and specificity receptors overexpressed on tumours. PRRNT employing the radiotagged somatostatin receptor agonists ^{90}Y-DOTATOC ([^{90}Y-DOTA^{0},Tyr^{3}]-octreotide) or ^{177}Lu-DOTATATE ([^{177}Lu-DOTA^{0},Tyr^{3},Thr^{8}]-octreotide or [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate) have been successfully used for the past 15 years to target metastatic or inoperable neuroendocrine tumours expressing the somatostatin receptor subtype 2. Accumulated evidence from clinical experience indicates that these tumours can be subjected to a high absorbed dose which leads to partial or complete objective responses in up to 30 % of treated patients. Survival analyses indicate that patients presenting with high tumour receptor expression at study entry and receiving ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC treatment show significantly higher objective responses, leading to longer survival and improved quality of life. Side effects of PRRNT are typically seen in the kidneys and bone marrow. These, however, are usually mild provided adequate

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protective measures are undertaken. Despite the large body of evidence regarding efficacy and clinical safety, PRRNT is still considered an investigational treatment and its implementation must comply with national legislation, and ethical guidelines concerning human therapeutic investigations. This guidance was formulated based on recent literature and leading experts' opinions. It covers the rationale, indications and contraindications for PRRNT, assessment of treatment response and patient follow-up. This document is aimed at guiding nuclear medicine specialists in selecting likely candidates to receive PRRNT and to deliver the treatment in a safe and effective manner. This document is largely based on the book published through a joint international effort under the auspices of the Nuclear Medicine Section of the International Atomic Energy Agency.

Keywords Peptide receptor radionuclide therapy · PRRNT · PRRNT, neuroendocrine tumours, guideline/s, renal protection

Purpose

This guidance document is aimed at assisting and guiding nuclear medicine specialists in:

1. Assessing patients with neuroendocrine tumours (NETs) for their eligibility to undergo treatment with ^{90}Y- or ^{177}Lu-radiolabelled somatostatin analogues.
2. Providing guidance on performing peptide receptor radionuclide therapy (PRRNT) and implementing this treatment in a safe and effective manner.
3. Understanding and evaluating the outcome of PRRNT, namely treatment results and possible side effects including both renal and haematological toxicities.

A committee of international experts was assembled under the auspices of the International Atomic Energy Agency (IAEA), in cooperation with the EANM Therapy, Oncology and Dosimetry Committees and with the Society of Nuclear Medicine and Molecular Imaging. They worked together to create this guidance document on the use of somatostatin analogue-based PRRNT. This guidance document was compiled taking into account recent literature and experts' opinion.

Regulatory issues

Applicable in all countries Clinicians involved in unsealed source therapy must be knowledgeable about and compliant with all applicable national and local legislation and regulations.

Applicable in the USA The radiopharmaceuticals used for the diagnostic and therapeutic procedures addressed in this guidance document are not approved by the Food and Drug Administration (FDA) in the USA. Therefore in the USA these procedures should be performed only by physicians enrolled in an investigational protocol pursuant to a valid Investigational New Drug application or Radioactive Drug Research Committee approval and under the purview of an appropriate institutional review board.

Background information and definitions

Definitions

PRRNT	PRRNT (or PRRT) involves the systemic administration of a specific well-defined radiopharmaceutical composed of a β-emitting radionuclide chelated to a peptide for the purpose of delivering cytotoxic radiation to a tumour. The oligopeptides are designed to target cellular proteins, commonly cell surface receptors, such as the somatostatin receptor (sstr) subtype 2 (sstr2) that is overexpressed on the cell surface of NETs in a tumour-specific fashion, thereby ensuring a high level of specificity in the delivery of the radiation to the tumour. Hence, PRRNT is a molecularly targeted radiation therapy, and thus is distinct from external beam radiation therapy.
Somatostatin	The naturally occurring somatostatin molecule is an oligopeptide comprising either 14 or 28 amino acids with a limited half-life in blood due to rapid enzymatic degradation. Somatostatin exerts an antisecretory endocrine and exocrine effect in addition to tumour cell-growth inhibition. Stabilized analogues of somatostatin (SSA) show prolonged duration of action [1].
Somatostatin receptors	In humans five sstr subtypes have been identified. Each sstr is a transmembrane molecule weighing approximately 80 kDa. Somatostatin exerts its action by inhibiting G-protein-dependent 3′,5′-cyclic monophosphate (cAMP) formation in a dose-dependent manner at subnanomolar concentrations. Sstr2 is overexpressed in NETs. Sstr2 is the key target molecule for both cold and radiolabelled SSA. Upon binding to its receptor, the complex (SSA-sstr) undergoes cellular internalization thereby

	enhancing the therapeutic effect of the radiolabelled drug [2].
Yttrium-90	The radiometal ^{90}Y is a pure β-emitting isotope with a physical half-life of 64 h. The maximum and mean β-particle energies are 2.28 MeV and 0.934 MeV, respectively. The maximum and mean β-particle penetration depths in soft tissue are 11 mm and 3.9 mm, respectively.
Lutetium-177	^{177}Lu is a β- and γ-emitting radionuclide with a physical half-life of 162 h (6.73 days). Compared to ^{90}Y, ^{177}Lu has lower maximum and mean β-particle energies (0.498 MeV and 0.133 MeV, respectively). These translate to maximum and mean soft-tissue penetration depths of 1.7 mm and 0.23 mm, respectively. ^{177}Lu has two main gamma emission lines: 113 keV (6 % relative abundance) and 208 keV (11 % relative abundance). The latter properties of ^{177}Lu allow posttreatment imaging and dosimetry assessments.
DOTATOC	DOTATOC is a derivatized somatostatin analogue peptide. DOTATOC is the abbreviated form of [DOTA0,Tyr3]-octreotide, where DOTA stands for the bifunctional chelating molecule 1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetic acid, and Tyr3-octreotide is the modified octreotide. This peptide shows a high affinity for sstr2 (IC_{50} 14±2.6 nM), but lower affinities for sstr5 (IC_{50} 393±84 nM) and sstr3 (IC_{50} 880±324 nM) [3].
DOTATATE	DOTATATE is also a derivatized somatostatin analogue peptide. DOTATATE is the abbreviated form of [DOTA0,Tyr3,Thr8]-octreotide or [DOTA0,Tyr3]-octreotate, and DOTA stands for the bifunctional metal-chelating molecule. This peptide shows a six- to ninefold higher affinity for sstr2 (IC_{50} 1.5±0.4 nM) than DOTA-TOC, but has no affinity for either sstr5 (IC_{50} 547±160 nM) or sstr3 (IC_{50} >1,000 nM) [4].

Background

NETs have proven to be ideal neoplasms for PRRNT, as the majority of these slow-growing malignancies overexpress sstrs. Appropriate candidates for PRRNT are patients presenting with well-differentiated or moderately differentiated neuroendocrine carcinomas, defined as NETs of grade 1 or 2 according to the WHO classification of 2010 [5]. The incidence of NETs has been rising over the past 30 years, particularly those arising from the midgut and pancreas [6]. The incidence of NETs in the USA rose from 10.9 to 52.4 per million between 1973 and 2004 (SEER database). NETs can occur in children and young adults, being diagnosed as early as at the age of 5 years, while their incidence increases with age. The clinical presentation may vary depending on the site of tumour origin. About 72 % of NETs arise in gastrointestinal structures, 25 % are bronchopulmonary in origin, and less than 5 % arise at other sites (e.g. thymus, breast and genitourinary system). Frequently, these tumours are discovered when metastatic or locally advanced and therefore inoperable. NETs can be either functioning or nonfunctioning in nature. Functioning tumours are associated with clinical syndromes, such as the carcinoid syndrome (due to the release of serotonin). Other secreting tumours include insulinomas (inducing hypoglycaemia), gastrinomas (inducing Zollinger-Ellison syndrome), VIPomas (associated with the watery diarrhoea, hypokalaemia and achlorhydria syndrome; WDHA syndrome).

Anatomical imaging of NETs should be as detailed and extensive as possible to provide accurate information about site and extent of the primary tumour, and the location and extent of regional and distant metastases. An exact assessment of liver metastases and degree of liver involvement using ultrasonography, CT or MRI is central for accurate staging and for assessing the response to treatment [7].

Functional imaging procedures applying sstr imaging using ^{111}In-pentetreotide (OctreoScan) with SPECT or PET with ^{68}Ga-labelled SSA, combined with morphological imaging procedures, are used to collect essential information for staging, assessing sstr status and making decisions on the most appropriate therapy regimens [8, 9]. Serial morphological examinations are mandatory to monitor therapy and detect recurrent disease. Emerging data indicate that ^{18}F-FDG PET may have additional prognostic value [10]. This information, however, needs validation in larger studies.

Multiple treatment approaches are now available for patients presenting with metastatic disease, considering recently introduced molecular targeted therapies and multimodality treatment options. For the choice of the most appropriate treatment, information regarding anatomical location and local invasion of adjacent structures, tumour functionality, sstr status, histological grading and staging are required to facilitate the decision-making process within the multidisciplinary tumour board. If the disease is restricted to the liver, surgical and locoregional approaches should be considered primarily. Chemotherapy is appropriate for highly proliferating NETs and pancreatic NETs, keeping in mind the fact that the vast majority of NETs are rather insensitive to this treatment.

Treatment options in NETs

Patients with NETs may present with local tumours, with or without regional or distant metastases. The common site of metastasis is the liver. These tumours may remain clinically silent until a significant liver tumour burden is present. Therapeutic options include surgery, SSA, interferon, chemotherapy, molecularly targeted agents, locoregional therapies and PRRNT. Supportive palliative care and pain control also play an important role in patient management. These options are not mutually exclusive and, for the most part, are interchangeable. Options of care, including PRRNT, should be chosen and implemented in a correct sequence by an experienced multidisciplinary team. This approach should provide the highest benefit while minimizing the risks and side effects and ensuring the best quality of life achievable for the patient. Surgery with curative intent should always be performed whenever feasible; in selected cases, and within a multidisciplinary approach, PRRNT may be beneficial as a neoadjuvant therapy to render a patient accessible to surgery. For functionally active tumours, cytoreductive strategies, e.g. transarterial chemoembolization (TACE), transarterial embolization (TAE), radiofrequency ablation (RFA) and other techniques such as selective internal radiation therapy (SIRT), should always be considered with the intention of ameliorating clinical symptoms. The optimal management of NETs is early surgical removal prior to the development of regional or distant metastases. Unfortunately, many patients are diagnosed with metastatic disease, when complete eradication of their tumours will not be possible. Removal of the primary tumour is indicated to prevent complications such as bleeding or small-bowel obstruction. Even in the presence of liver metastases, removal of the primary tumour has several advantages and seems to have a positive prognostic impact on survival [11–14]. Solitary or isolated liver metastases can be surgically removed, while a more diffuse liver infiltration is usually treated using a locoregional approach.

Locoregional approaches or local ablative therapies target predominantly liver metastases aiming at achieving local tumour control and alleviating functional secretory syndromes. Different techniques are applied depending on individual findings (number size and distribution of liver lesions, their morphology, focal or diffuse, and their vascularization), functional activity of the NET and locally available expertise. In an individual with few liver lesions with a preferably resected primary lesion, liver lesions can be treated by surgical resection with or without RFA or laser-induced interstitial thermoablation. In those with multifocal or diffuse liver disease causing a high tumour load, TACE and TAE are the preferred choices [15, 16]. Local embolization techniques are particularly useful when treating patients with functionally active liver metastases. Following TACE, symptomatic response rates of 60–95 % and biochemical response rates of 50–90 % are achieved and radiological response of 33–80 % have been reported [17–19]. Response duration is between 18 and 24 months. Similar response rates are achieved with TAE alone [16]. In general, the procedure may require more than one treatment session to ensure effectiveness and consolidation of the treatment and to minimize the risk of complications.

The recently introduced SIRT has shown variable response rates among individual centres [20]. Prospective studies are however lacking. In a single prospective study in 34 patients the objective response rate was 50 % [19]. Given the lack of comparative studies of the different techniques used for local ablative and locoregional therapies, the choice of technique will be highly dependent on the physicians' experience in the different centres and on individual criteria such as number, size, vascularization and distribution of the lesions.

Among the medical treatments, octreotide and lanreotide are the two most used sstr agonists. They play an essential role in the control of both symptomatic and asymptomatic NETs and should be regarded as first-line therapy. SSA can be used with virtually all of the other therapeutic options available. As the vast majority (87–92 %) of NETs express sstr2, patients should always be offered this therapy alongside other concurrent therapeutic options, and for supportive care. Long-acting SSA possess secretory inhibiting action, and are approved for alleviating the symptoms of the carcinoid syndrome, such as flushing and diarrhoea or bronchial obstruction, and to prevent carcinoid crisis. It is reported that treatment with SSA may control the clinical syndrome in 40–90 % of patients subject to tumour load and dosage [21, 22]. Nevertheless, patients may become refractory to syndrome control, and need incremental dosage increases of SSA. However, most patients with tumour progression require an additional treatment, including the use of PRRNT. The recent PROMID study conducted in Germany showed the effectiveness of long-acting SSA as an antiproliferative therapeutic agent in midgut NET. In this study, time to tumour progression in patients given octreotide LAR 30 mg intramuscularly monthly was more than double that in patients receiving only placebo (6.0 vs. 14.3 months). The NCCN guidelines and very recently the ENETS guidelines have added octreotide as an option for antiproliferative treatment [23, 24].

Interferon-alpha (IFN-α) has been used for treating patients with NETs, especially those with the carcinoid syndrome, for more than 25 years. It is considered the main antisecretory drug used for the treatment of functional tumours [25]. IFN-α effectively reduces hypersecretion-related symptoms in patients with carcinoid syndrome in a similar manner to SSA. Partial tumour growth responses are also observed in 10–15 % of patients with malignant

carcinoids, and stabilization in 39 %. IFN-α has also been demonstrated to be effective in endocrine pancreatic tumours [26]. The very common side effect of IFN-α, namely a 'flu-like syndrome, limits both the use of high dosages and the duration of treatment due to intolerance forcing its interruption. Systemic chemotherapy is effective in some patients, especially those with poorly differentiated NET/neuroendocrine carcinoma (grade 3, WHO 2010) or progressive NET of the pancreas. However, in well-differentiated midgut NETs/NETs (grade 1/2, WHO 2010) the response rates to chemotherapy are low (7–20 %) and a survival advantage has not been demonstrated [27, 28]. The standard treatment for neuroendocrine carcinoma (grade 3) is cisplatin and etoposide. The response rate with this combination is 42–67 %, and its duration is often short, ranging from 8 to 9 months [32]. The combination of irinotecan and cisplatin [29] or FOLFOX chemotherapy (5-fluorouracil or capecitabine and oxaliplatin) may be an alternative [30]. PRRNT is very rarely a suitable treatment option for neuroendocrine carcinoma (grade 3), because of the low expression of sstr but it may be considered following the failure of chemotherapy and if ^{111}In-pentetreotide (OctreoScan) or ^{68}Ga-DOTATOC/DOTATATE PET/CT demonstrates moderate to high sstr expression.

Systemic chemotherapy based on streptozotocin (Zanosar, STZ) is considered a standard therapy for progressive pancreatic NETs with low or moderate proliferative capacity. Combinations of STZ and 5-fluorouracil and/or doxorubicin have been shown to lead to partial remission rates of 35–40 % [31–33]. Recent phase II studies have shown efficacy of temozolomide based chemotherapy either with antiangiogenic drugs or capecitabine [34, 35]. Standards of care for the use of chemotherapy have been defined by ENETS [36]. In recent years, the efficacy of molecular targeted therapies for treating NETs has been assessed in clinical trials. These therapies include angiogenesis inhibitors, single or multiple tyrosine kinase inhibitors and the novel SSA analogue pasireotide, for which clinical trials are ongoing. The drugs with the highest evidence of efficacy are sunitinib and everolimus (RAD-001). Both lead to extension of progression-free survival (PFS) of patients with advanced pancreatic NET. For everolimus, an mTOR inhibitor, there is evidence of efficacy in controlling NET arising from other sites associated with the carcinoid syndrome [37]. The most developed antiangiogenic drugs are sunitinib and the anti-VEGF antibody bevacizumab. In a phase II study bevacizumab in combination with octreotide LAR led to partial tumour remission in 18 % of patients and stable disease in 77 % [38]. A recent international phase III study of sunitinib versus placebo in patients with progressive well-differentiated endocrine pancreatic tumour was interrupted prematurely due to the striking superiority of sunitinib evident by a PFS of 11.1 vs. 5.5 months [39]. The objective remission rate was less than 10 %. The drug was recently approved by the US FDA and the European Medicines Agency for the treatment of advanced and progressive well-differentiated pancreatic NETs.

Everolimus has been studied in more than 1,000 patients with NET and has been included in several clinical trials (RADIANT-1, RADIANT-2, RADIANT-3 trials, RAMSETE trial). Antitumour activity of everolimus has been confirmed in RADIANT-1 in patients with progressive metastatic pancreatic NETs after failure of at least one line of cytotoxic chemotherapy. The trial studied 160 patients divided into two groups with or without monthly intramuscular octreotide acetate therapy. The combination therapy group showed significantly longer PFS (16.7 vs. 9.7 months) [40]. The efficacy of everolimus has been confirmed in a large international placebo-controlled trial including 410 patients with progressive pancreatic NET (RADIANT-3) [41]. Everolimus significantly reduced the risk of disease progression and led to a prolongation of PFS by 6.4 months (11 vs. 4.6 months) compared to placebo. Objective tumour response was low (4.8 % partial remissions). Disease control rate (partial response + stable disease) was, however, higher with everolimus than with placebo with best supportive care (77.7 % vs. 52.7 %). Side effects were rarely grade 3 or 4; the most frequently reported side effects included stomatitis, anaemia and hyperglycaemia. In May 2011 the US FDA approved everolimus for the treatment of progressive NETs of pancreatic origin in patients with nonresectable, locally advanced, or metastatic disease.

In the global supportive approach to the patient, and when delivering PRRNT, nutrition and pain control are an essential component of care. Treatment of pain in patients with NET follows the general principles followed in adult and paediatric oncology [42]. Effective treatment of NETs, such as PRRNT, may alleviate pain, including bone pain. Treatment of painful bone metastasis is also mandatory with the administration of bisphosphonates as supportive therapy.

PRRNT a historical overview

PRRNT using radiolabelled octreotide was first attempted in the 1990s. The initial phase I trial investigated the safety and efficacy of using high activities of the diagnostic compound ^{111}In-octreotide as a therapeutic radiopharmaceutical. The results in terms of clinical efficacy were attributed to the effect of intracellular emission of the Auger and conversion electrons by ^{111}In following the internalization of the peptide–receptor complex. Partial remissions were exceptional, and furthermore three patients developed leukaemia or myelodysplastic syndrome from the group receiving the highest cumulative dose (90–100 GBq) [43]. In Europe, ^{111}In-pentetreotide was abandoned as a therapy option in favour of the more efficient β emitters ^{90}Y and ^{177}Lu. ^{111}In-pentetreotide is,

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