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Neuroendocrine Cancers (JR Strosberg, Section Editor)

Peptide Receptor Radiotherapy: Current Approaches and Future Directions

Grace Kong, MBBS (Hons), FRACP, FAANMS[1,2,*]
Rodney J. Hicks, MBBS (Hons), FRACP, MD[1,2]

Address
[*,1]Department of Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria, Australia
Email: Grace.kong@petermac.org
[2]The Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria, Australia

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Opinion statement

Neuroendocrine neoplasia (NEN) represents a heterogenous group of tumours. Guidelines regarding treatment choice and sequencing remain complex given varied primary sites, hormone-secretory status, tumour grade, disease heterogeneity, and paucity of rigorous comparative trials due to rarity of this condition. However, there is increasing evidence that peptide receptor radionuclide therapy (PRRT) is an effective treatment, especially for grade 1 and 2 NEN. Primary indications for treatment include oncologic control in patients with progressive disease and symptomatic control in the context of hormone-secretory syndromes or tumour-related pain. However, strategies are needed to further optimize efficacy and outcomes, and to expand treatment indications. Important considerations could include personalized PRRT regimens based on better characterization of the disease in an individual patient. Future directions should also focus on strategies to further enhance the efficacy of PRRT including combination treatments with other systemic therapies, such as radiosensitising chemotherapy, DNA repair–modifying agents and immunotherapy. Further evolution of therapeutic radiopharmaceuticals also offers promise.

Introduction

Peptide receptor radionuclide therapy (PRRT) delivers highly localised radiation by targeting somatostatin peptide receptors (SSTR) on specific tumour cells [1••]. This therapy has been introduced over the past two to three decades, primarily for the treatment of unresectable/metastatic well-differentiated neuroendocrine neoplasms (NEN). These tumours typically have high SSTR expression allowing targeted PRRT. NEN represents a rare heterogenous group of tumours arising from the diffuse endocrine system, most typically from gastroenteropancreatic (GEP) origins, and also from the bronchopulmonary system or thymus. Although each individual subtype has a low incidence, the total number of new diagnoses of NEN is increasing worldwide [2, 3•].

PRRT is comprised of three main components: a high activity radionuclide (Table 1), linked to a chelator (DTPA or DOTA), which binds to a SSTR-binding ligand, which is typically a somatostatin analogue. Initial evaluation of PRRT utilized ^{111}In, which emits Auger electrons with a short tissue penetration range (maximum 10 μm) [4]. This radionuclide demonstrated relatively low objective response rates [5, 6], and when combined with high cost and limited availability have restricted its routine clinical use. ^{90}Y emits the most energetic beta particles with maximum penetration range of 12 mm [4], resulting in favourable objective response rates of 10–30%, but with moderate toxicity, particularly nephrotoxicity which tends to occur when renoprotective amino acid infusions are not used [7, 8]. ^{177}Lu has a favourable intermediate beta particle emission (maximum penetration of 3 mm) [4] achieving similar objective responses but with limited toxicity compared with ^{90}Y-labelled PRRT. Hence, ^{177}Lu PRRT is currently the radionuclide of choice in most circumstances. For PRRT to be effective, all lesions must have high SSTR expression to enable adequate therapeutic targeting. This characteristic is detected by molecular imaging techniques with conventional ^{111}In-octreotide scintigraphy, or with the more sensitive technique of ^{68}Ga-based PET/CT [9]. This article provides an update of the current role of PRRT focusing on the treatment of NEN, as well as outlining some potential future developments and directions in this field.

PRRT for neuroendocrine neoplasia—current evidence

PRRT has been used by many centres worldwide for the treatment of NEN for the last two to three decades; however, due to the rarity and heterogeneity of disease,

Table 1. Physical properties of radionuclides potentially applicable for radionuclide therapy for NEN

Radionuclide	Half-life	Emissions	Mean energy (keV)	Maximum tissue penetration range	Source
Indium-111	2.81 days	Conversion electrons	245	550 μm	Cyclotron
		Auger electrons	25	10 μm	
		Gamma rays	171, 245		
Yttrium-90	2.67 days	Beta particles	934	12 mm	Generator
Lutetium-177	6.65 days	Short beta gamma rays	149 208	3 mm	Reactor
Copper-67	2.58 days	Beta particles Gamma rays	121 184	2–3 mm	Reactor/cyclotron
Bismuth-213	45 min	Alpha	8320	84 μm	Generator
Actinium-225	10 days	Alpha	6800	61 μm	Accelerator

few rigorous multicentre trials have been performed. Direct comparison of outcomes has been challenging due to variation in patient eligibility, varying treatment protocols, and inconsistent outcome and follow up measures used between different centres. Nonetheless, there is a relatively high consensus regarding the effectiveness of PRRT for SSTR positive GEP NEN, with evidence of encouraging morphologic responses, disease control rates, overall progression-free survival (PFS), and overall survival (OS) [1••].

The NETTER-1 study was the first prospective randomised trial to confirm the efficacy of PRRT [10••]. This phase III trial involved a 1:1 randomisation of 229 patients with progressive metastatic small intestinal NEN (grade 1 or 2, Ki67 < 20%) on monthly Sandostatin LAR 30 mg, to either dose escalation of octreotide LAR to 60 mg, versus ^{177}Lu-dotatate + Sandostatin LAR 30 mg. The PRRT protocol involved 4 cycles of 7.4 GBq of ^{177}Lu-dotatate at 8-week intervals. Median PFS was not reached with ^{177}Lu-dotatate compared with 8.4 months for the high-dose octreotide LAR arm ($p < 0.001$). The interim analysis indicated that the estimated risk of death was 60% lower in the PRRT arm than the control group ($p = 0.004$; hazard ratio 0.40). The objective response rate was also superior in the PRRT arm: 18% versus 3% ($p < 0.0004$). Final analysis of long-term outcome is not yet available. These prospective results provide strong evidence confirming the effectiveness of ^{177}Lu-dotatate PRRT in SSTR-positive small intestinal NEN, in keeping with other phase I–II institutional studies and retrospective analyses of many single institutional experiences (Fig. 1).

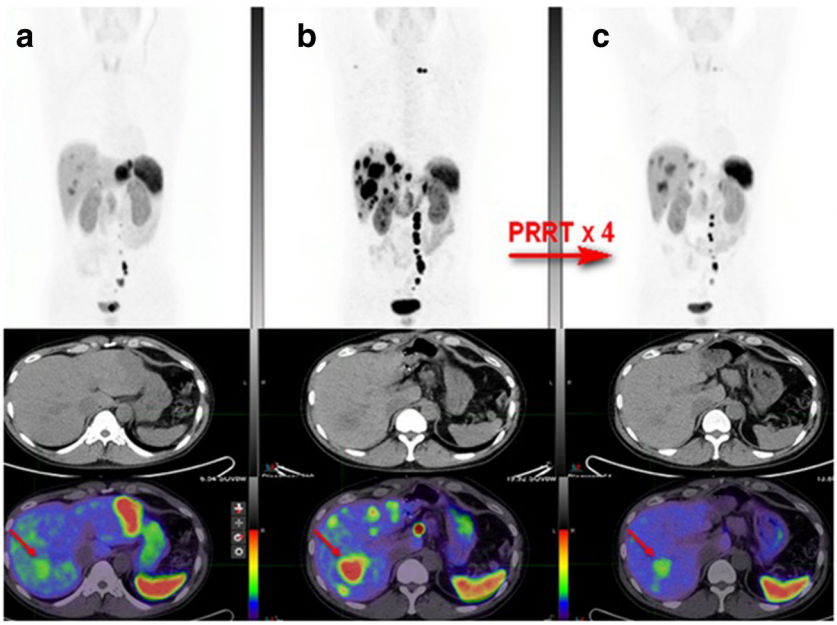

Fig. 1. Case illustrating significant imaging response from PRRT. Top row: ^{68}Ga-DOTA-octreotate PET/CT maximum intensity projection (MIP images); middle row: unenhanced CT component of PET/CT; bottom row: corresponding trans-axial fused images. Fifty-year-old female with G2 small intestinal NEN (Ki-67 of 12%) and hepatic and nodal metastases (column A). Disease progressed despite somatostatin analogue (SSA) therapy (column B) with increasing tumour burden, number, and size of lesions. Due to high SSTR expression and progressive disease, 4 cycles of ^{177}Lu-DOTATATE PRRT were given, achieving a significant reduction in tumour burden post-PRRT on ^{68}Ga-DOTA-octreotate PET/CT (column C). Red arrows highlight an index liver lesion on trans-axial images which progressed in size following SSA but regressed after PRRT treatment.

The evidence base for PRRT in metastatic NEN from pancreatic origin is also encouraging but currently limited to single institutional and largely retrospective reports with treatment generally administered on a compassionate basis. For example, Ezzidin et al. analysed 68 patients with progressive and advanced grade 1 or 2 pancreatic NEN treated with ^{177}Lu-dotatate showing a PFS of 34 months with reversible grade 3 or higher haematotoxicity in 5.9% and no significant nephrotoxicity [11]. PRRT may also play a role in neoadjuvant use for patients with unresectable or borderline resectable primary pancreatic NEN [12, 13].

The results of the NETTER-1 trial and other institutional series have recently led to regulatory approval of ^{177}Lu-dotatate in the USA and in several European countries for patients with progressive metastatic GEP NEN. PRRT is also widely used in other jurisdictions both for NEN and other indications under compassionate use guidelines. Treatment indications and approvals are likely to expand in the future as prospective trials provide further supporting evidence.

Regarding side effects, PRRT is generally well tolerated with limited acute and medium-term toxicity profiles. Potential acute side effects include nausea and vomiting, which is usually attributed to amino acid infusion used for renal protection but can be readily prevented with the use of 5-HT-3 antagonists. Hyperkalaemia can be associated with amino acid infusion, and the use of a loop diuretic during infusion could be considered to enhance potassium excretion in patients with levels in the upper end of the normal range [1••]. Lethargy, flare of symptoms including increasing pain or discomfort secondary to tumour swelling or worsening of hormone secretory symptoms (such as flushing or diarrhoea) can occur due to release of pre-formed hormones from cellular damage, but these symptoms are usually transient and most pronounced after the first cycle [1••, 14]. Hormone crisis is rare and reported in < 1%. Temporary mild hair loss has been described in 60% of patients [1••]. In the prospective NETTER-1 trial, treatment was well tolerated overall with the most documented side effects consisting of grade 1–2 nausea and vomiting, attributable to commercial amino acids used for renal prophylaxis. There was no excess acute nephrotoxicity observed in the ^{177}Lu-dotatate arm.

Side effects of greatest long-term concern include potential renal and marrow toxicity. ^{90}Y is considered more nephrotoxic due to the longer range of its beta particle. A recent large series of 807 patients found that treatment with ^{90}Y or combined ^{90}Y+^{177}Lu was more likely to result in nephrotoxicity than treatment with ^{177}Lu alone, but severe renal complications were uncommon (1.5%) [15]. Long-term follow-up by other groups has also demonstrated low rates of nephrotoxicity from ^{177}Lu when used with amino acids [1••].

Subacute grade 3 or 4 haematological toxicities have been reported to occur in up to 11% of patients [16]. The incidence for therapy-related myeloid neoplasms (t-MN) including myelodysplasia (MDS) or acute (AL) leukaemia ranges from 1 to 5.4% [15, 17–19], but underlying mechanisms remain poorly understood. Bodei et al. reported an incidence of MDS/AL of 3.45% in the largest yet-reported cohort of 807 patients. Variables most significantly associated with these events were duration of PRRT and platelet toxicity grade during treatment. No other definite patient- or treatment-associated factors were identified, raising the possibility of pre-existing biological or genetic susceptibility as potential contributing factors, which would require further prospective investigation. In the NETTER-1 study, 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 MDS was attributed to PRRT, but longer-term follow-up is not yet available [10••].

PRRT for symptom control

A proportion of NEN can secrete active hormones causing specific clinical syndromes. Up to 13% of small bowel NEN secrete serotonin resulting in carcinoid syndrome characterised by flushing, diarrhoea, and bronchospasm [20]. Hormone-secretory symptoms as well as tumour-related pain often lead to a reduced quality of life (QOL) for these patients compared with the general population and can significantly affect overall function [21, 22]. Somatostatin analogues (SSA) are usually effective as first-line treatment to reduce hormone secretion [23, 24]. Improvement in QOL has been reported in several single-arm PRRT studies [25–27]. One of the largest series, including 265 NEN patients treated with ^{177}Lu-dotatate, reported significant improvement on the EORTC QLQ C-30 scale in global health status, QOL, Karnosfsky performance score, and symptoms including diarrhoea [28]. Prospective data from the NETTER-1 trial also demonstrated significant QOL benefit for patients with progressive midgut NEN compared with high-dose LAR control arm, particularly with significant delay in time to deterioration in key QOL domains including global health, physical functioning, role functioning, diarrhoea, pain, and fatigue [10••].

The majority (60–90%) of pancreatic NEN are non-functioning tumours, but a small proportion can secrete specific hormones causing distinct functional syndromes. The most typical are gastrinoma, insulinoma, and glucagonoma. Other less common hormone syndromes relate to secretion of vasoactive intestinal peptide (VIP), adrenocorticotropic hormone (ACTH), growth hormone–releasing hormone (GHRH), parathyroid hormone–related peptide (PTHrP), and others [20, 29, 30]. Despite reports mainly generated from small retrospective institutional series, there is increasing evidence supporting the efficacy of PRRT in treating functional syndromes and achieving oncologic control from pancreatic NEN, particularly for gastrinomas, glucagonomas, and insulinomas [20, 31–35]. Further larger multicentre PRRT trials are needed to confirm the utility of PRRT in these rare subgroups.

Future directions

Expanding indications—prospective trials

Based on the prospective NETTER-1 trial and results from multiple previous institutional series, ^{177}Lu-dotatate has now been approved for use for progressive grade 1 and 2 GEP NEN in the USA and many countries in Europe. However, provided that SSTR expression is retained, there is increasing evidence that PRRT is also effective in a subset of patients with grade 3 NEN, particularly in those with Ki-67 of 21–55%, or well-differentiated, SSTR-positive G3 NET. It is increasingly recognized that these patients respond poorly to 'standard' platinum-etoposide chemotherapy [36–40]. The NORDIC study showed that NEN with Ki67 of 21–55% has lower responses to platinum-etoposide than those with Ki67 > 55% (15% vs 42%), despite having a superior median OS

(14 months vs 10 months) [41]. A recent retrospective Australian study (28 patients) suggested promising responses from PRRT in similar patients, with an impressive OS of 46 months for the Ki-67 ≤ 55% subgroup [42•]. Nicolini et al. reported median PFS of 23 and OS 52 months, with disease control rate of 70% with PRRT [43]. A subsequent retrospective multicentre Scandinavian series of 149 also showed favourable median OS 31 months in the subgroup of patients with Ki 67 of 21–55% [44•]. Therefore, further prospective multicentre studies are warranted to confirm efficacy and to expand indications for PRRT in this poor prognostic G3 subgroup.

The more rapid proliferation of higher grade tumours may require closer spacing of treatment cycles to avoid early repopulation of cancer cells between treatments, whereas low-grade tumours may take longer to come back into cycle. It has long been recognized that actively growing cells are more susceptible to cytotoxic therapies, and timing of treatment cycles to coincide with restitution of growth may be important for treatment response as well as durability of disease control.

Personalized versus standardized treatment

To date, there is no consensus regarding the optimal treatment protocol with variable opinion in relation to the type of radiopharmaceutical, the administered activity, the number of cycles, the time interval between cycles, or the best method for response assessment. Protocols vary between countries and centres. These partly depend on local regulations, funding mechanisms, logistics of radiopharmaceutical supply, and experience. Most centres, however, use a standard PRRT regimen based on the initial protocol developed by the Erasmus Medical Center in Rotterdam. This includes 4 cycles of a single agent of fixed administered activity of 7.4 GBq (200 mCi), administered 8 weeks apart regardless of patient or disease characteristics. This was the protocol adopted by the NETTER-1 trial. However, the significant heterogeneity in disease distribution, grade, phenotype, and tumour burden as well as patient-related features including body mass and renal function may influence both bioavailability to tumour and off-target radiation exposure. These variations could justify development of a more personalized approach [45]. One consideration is the choice and sequencing/combination of currently available therapeutic radionuclides to optimize therapy to lesions of different sizes. ^{90}Y has theoretical advantages for larger lesions due to its long β-particle path length whilst ^{177}Lu may be better suited to smaller lesions [46].

Results of combination therapy are encouraging [1••, 47, 48]. Using ^{90}Y-PRRT upfront, the "tumor sink effect" in high disease burden can limit radiation exposure to normal organs; sequencing with subsequent ^{177}Lu-dotatate in patients with bulky but responding tumours may allow greater upfront radiation dose to tumour, whilst limiting potential associated toxicity [35]. However, these approaches require further validation.

Whilst no prospective comparative studies are yet available, patients with liver-dominant disease may benefit from hepatic arterial administration rather than use of the conventional intravenous administration [49, 50]. Further trials are warranted. Agents with Auger electron or alpha particle decay also have potential advantages for the treatment of micro-metastatic disease and may particularly play a role in diffuse infiltrative disease. ^{111}In-PRRT is an example of

the former type of physical decay whereas alpha-emitting radionuclides are discussed later.

Another consideration is the variation of administered activity, number of cycles, and time interval between cycles according to disease and patient factors. It has previously been shown that tumour sequestration is a major factor leading to a 'sink effect' that decreases activity in non-target organs such as the kidneys [51]. This supports the rationale for potentially administering higher administered activity to patients with higher tumour burden. The role of prospective quantitative dosimetry is an important aspect for future investigation and development, to better define administered activity to maximize tumour dose whilst limiting physiologic exposure/toxicity to provide personalized calculated administration of PRRT. The currently used ^{68}Ga-labelled PET tracer provides excellent diagnostic quality, but its short physical half-life of 68 min significantly limits its ability to perform multi-time point or delayed imaging for dosimetry purposes. Further diagnostic tracers of longer half-life or theranostic pairs such as ^{64}Cu/^{67}Cu could potentially be beneficial and are currently being investigated [52].

Combination therapies with PRRT

To further enhance effectiveness of radiation-induced damage from PRRT, combining PRRT with radiosensitising treatments can be considered. Several studies have used concomitant chemotherapy including infusional 5FU or oral capecitabine [6, 53–56], or capecitabine + temozolomide [57] with favourable responses and acceptable toxicity for patients with metastatic NEN, but there is lack of prospective data to compare against PRRT alone, despite some studies being currently underway. Another novel approach is combination of PRRT with poly ADP ribose polymerase (PARP) inhibitors to reduce the efficacy of single-strand DNA-break repair. Preliminary pre-clinical data suggest this combined regimen significantly enhances PRRT-induced cell death with increase of DNA double-strand breaks compared with ^{177}Lu-dotatate alone, and results in significant reduction in tumour volume [58]. A prospective phase I clinical trial is being planned in Australia to evaluate this novel combination to enhance PRRT efficacy in NEN patients. The possibility of increasing immune recognition of NEN through cellular radiation damage and subsequent neoantigen presentation provides an attractive rationale for combining PRRT with immune checkpoint therapy. A proof-of-concept study using PRRT with immunotherapy is being performed in Merkel cell carcinoma, a disease with neuroendocrine features including SSTR expression in a proportion of cases.

New developments—peptide, radionuclide, and receptor targeting

New peptide

There is evidence that radiolabelled SSTR2 antagonists (as opposed to agonists) generate higher tumour doses and more DNA double-strand breaks than agonists, resulting in better treatment efficacy despite poor internalization [59]. ^{177}Lu-DOTA-JR11 (^{177}Lu-OPS201) is currently being evaluated in a phase 1–2 multicentre study (ClinicalTrials.gov identifier NCT02592707) and in a theranostic study of the associated ^{68}Ga-diagnostic agent (ClinicalTrials.gov identifier: NCT02609737).

New radionuclide

Alpha particle-emitting radionuclide therapies are also being developed and generating interest, with advantages of very high energy deposition and a short path length of 40–100 μm, equivalent to the thickness of 1–3 cell widths. The short therapeutic range leads to high intracellular accumulation of the alpha particle and a higher chance of target damage to the cell's nucleus [60•]. Early experience with alpha emitters has shown effectiveness in prostate cancer among patients refractory to ^{177}Lu prostate-specific antigen treatment [61, 62], but its clinical evidence in NEN is sparse. The two principal therapeutic alpha radionuclides used in preclinical- and clinical-targeted therapy of SSTR tumours are Bismuth-213 (^{213}Bi) and Actinium-225 (^{225}Ac) (Table 1). Another alpha-emitting radionuclide is Lead-212 (^{212}Pb). ^{213}Bi has a short half-life of 45 min and can be produced from a ^{225}Ac/^{213}Bi generator, but the short half-life would require an on-site radiopharmacy to produce the compound. The short half-life of ^{213}Bi could have some advantages given the higher dose rates. ^{213}Bi has been successfully labelled with DOTA peptides with > 99% purity in preclinical and clinical studies [63, 64]. Alternatively, ^{225}Ac has a longer half-life of almost 10 days. Several pre-clinical studies using both ^{213}Bi- and ^{225}Ac-labelled SSTR therapy have been performed [60•]. The first-in-human study in NEN was published in 2014 by the Heidelberg group [63]. They presented 8 patients with progressive NEN refractory to ^{90}Y/^{177}Lu-DOTATOC treatment, subsequently treated with ^{213}Bi-DOTATOC (7 patients treated with intra-arterial administration) showing enduring responses in all treated patients (1 complete response, 3 partial response, 3 stable disease, and 1 not evaluable). Moderate chronic kidney toxicity was observed (mean reduction of glomerular filtration rate 30%), and acute haemotoxicity was less pronounced than with preceding beta therapies. Formal prospective trials are needed to assess the promising efficacy of alpha-emitting radiolabelled SSAs. A phase 1 study of ^{212}Pb-DOTAMTATE (AlphaMedixTM) for SSTR+ NEN is underway (NCT03466216).
Other radionuclide theranostic pairs of interest include ^{64}Cu/^{67}Cu and ^{44}Sc/^{47}Sc. ^{161}Tb is a combined beta and Auger electron emitter and may provide radiation to both larger and microscopic tumour deposits [65].

Multiple receptor targets

The presence of tumour-specific receptors allow direct therapeutic targeting with radionuclide therapy, as exemplified by PRRT targeting SSTR on NEN cells. Whilst SSTR remain the dominant target for well-differentiated NEN, tumour heterogeneity exists, and some tumours can express multiple receptors concomitantly. For instance, in vitro studies have shown in addition to SSTR, other peptide receptors such as glucagon-like peptide 1 (GLP-1) receptor are overexpressed in insulinomas, and glucose-dependent insulinotropic polypeptide (GIP) receptor and cholecyctokinin-2 (CCK2) receptors are overexpressed in GEP NENs [66]. In particular, CCK-2 receptors are over-expressed on numerous tumours including medullary thyroid cancer [67–69] and insulinoma [70].This may represent an important molecular target for NEN with low or absent SSTR expression. Interestingly,

54.5% of all NEN patients with disease negative on SSTR-2 imaging were found to have positive uptake on CCK-2 imaging [67]. Further advances in the development of radiolabelled CCK-2 PET imaging, with potential theranostic application for patients with low SSTR-expressing, are expected. Through discovery of more NEN-specific targets, future directions with multireceptor targeting could potentially be achieved by multivalent ligands, cocktails of ligands, or sequential radioligand administration for tumours with heterogeneity and multireceptor expression.

PRRT for other tumours with high SSTR expression

Apart from GEP NEN, other tumours that are known to express SSTR include pheochromocytoma and paraganglioma (PPGL), neuroblastoma, meningioma, Merkel cell carcinoma, medullary thyroid cancer, and small cell lung cancer [1••]. There is emerging evidence that PRRT can be effective for some of these conditions in the context of high SSTR expression. In particular, several retrospective series for patients with SSTR-positive PPGL treated with PRRT showed low toxicity, favourable disease control [71–75], and symptomatic as well as biochemical response in patients with functional disease. In one study, 62% PPGL patients were able to reduce antihypertensive medications at 3 months post-treatment, providing a very promising therapeutic option for patients with uncontrolled malignant hypertension [76]. There is also emerging evidence that PRRT is safe and feasible for paediatric patients with SSTR-positive metastatic neuroblastoma [77–79], supporting further prospective clinical trials in these patients. A prospective phase 2 trial (LuDO Trial) has been conducted in the UK; results are yet to be formally published. A subset of patients with small cell carcinoma may also have high SSTR expression. Combined ^{177}Lu-dotatate PRRT + carboplatin/etoposide has shown significant reduction of tumour volume and improved median overall survival compared with PRRT or carboplatin/etoposide alone in a pre-clinical study, and significant responses have been demonstrated in early clinical experiences, warranting further prospective evaluation for these patients with otherwise poor prognosis [80].

Conclusion

There is no doubt that PRRT is an effective treatment modality with an increasing role for selected patients with SSTR expressing NEN. This treatment is generally well tolerated but infrequent complications and toxicity can occur and need to be considered in the context of individual patient and disease characteristics. Efficacy from PRRT can be optimised to further improve the outcome of patients with these complex heterogenous diseases. Future studies should focus on performing well-designed prospective trials and incorporating patient-reported outcomes, ideally with multicentre participation. Multiple potential new developments are underway to further improve theranostic applications, including strategies which allow for a more personalized approach. These include developments in dosimetry, novel combination treatments, new and radionuclides, new ligands, and new NEN targets. Clearly, multidisciplinary and collaborative efforts are required to establish the role of PRRT and to generate new discoveries and developments, with the aims of improving patient outcomes.

Compliance with Ethical Standards

Conflict of Interest

Grace Kong declares that she has no conflict of interest.

Rodney J. Hicks was issued shares in Telix Pharmaceuticals at its IPO as a member of its scientific board. These shares are held on behalf of Dr. Hicks' institution; therefore, he receives no financial benefit from this holding.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Hicks RJ, Kwekkeboom DJ, Krenning E, Bodei L, Grozinsky-Glasberg S, Arnold R, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. Neuroendocrinology. 2017;105(3):295–30.

Recent international ENETS guidelines providing comprehensive overview, evidence and approaches for the use of PRRT in patients with NEN.

2. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72.

3.• Leoncini E, Boffetta P, Shafir M, Aleksovska K, Boccia S, Rindi G. Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. Endocrine. 2017;58(2):368–79.

Large review showing increasing incidence of NEN worldwide involving most anatomical sites and grades.

4. Dash A, Chakraborty S, Pillai MR, Knapp FF Jr. Peptide receptor radionuclide therapy: an overview. Cancer Biother Radiopharm. 2015;30(2):47–71.

5. Teunissen JJ, Kwekkeboom DJ, Valkema R, Krenning EP. Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr Relat Cancer. 2011;18(Suppl 1):S27–51.

6. Kong G, Johnston V, Ramdave S, Lau E, Rischin D, Hicks RJ. High-administered activity In-111 octreotide therapy with concomitant radiosensitizing 5FU chemotherapy for treatment of neuroendocrine tumors: preliminary experience. Cancer Biother Radiopharm. 2009;24(5):527–33.

7. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol. 2011;29(17):2416–23.

8. Bodei L, Cremonesi M, Grana CM, Chinol M, Baio SM, Severi S, et al. Yttrium-labelled peptides for therapy of NET. Eur J Nucl Med Mol Imaging. 2012;39(Suppl 1):S93–102.

9. Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine and hybrid imaging. Neuroendocrinology. 2017;105(3):212–44.

10.•• Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of 177Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125–35

First prospective phase 2 study confirming efficacy of PRRT in patients with midgut NEN compared with high-dose SSA. Results from this pivitol study and from prior multiple institutions have led to approval of ^{177}Lu-DOTA-octreotate (LuTathera) in USA and many countries in Europe.

11. Ezziddin S, Khalaf F, Vanezi M, Haslerud T, Mayer K, Al Zreiqat A, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014;41(5):925–33.

12. Barber TW, Hofman MS, Thomson BN, Hicks RJ. The potential for induction peptide receptor chemoradionuclide therapy to render inoperable pancreatic and duodenal neuroendocrine tumours resectable. Eur J Surg Oncol. 2012;38(1):64–71.

13. van Vliet EI, van Eijck CH, de Krijger RR, Nieveen van Dijkum EJ, Teunissen JJ, Kam BL, et al. Neoadjuvant treatment of nonfunctioning pancreatic

neuroendocrine tumors with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med. 2015;56(11):1647–53.
14. de Keizer B, van Aken MO, Feelders RA, de Herder WW, Kam BL, van Essen M, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2008;35(4):749–55.
15. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015;42(1):5–19.
16. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014;15(1):e8–21.
17. Bergsma H, Konijnenberg MW, Kam BL, Teunissen JJ, Kooij PP, de Herder WW, et al. Subacute haematotoxicity after PRRT with (177)Lu-DOTA-octreotate: prognostic factors, incidence and course. Eur J Nucl Med Mol Imaging. 2016;43(3):453–63.
18. Kesavan M, Turner JH. Myelotoxicity of peptide receptor radionuclide therapy of neuroendocrine tumors: a decade of experience. Cancer Biother Radiopharm. 2016;31(6):189–98.
19. Goncalves I, Burbury K, Michael M, Iravani A, Ravi Kumar AS, Akhurst T, et al. Characteristics and outcomes of therapy-related myeloid neoplasms after peptide receptor radionuclide/chemoradionuclide therapy (PRRT/PRCRT) for metastatic neuroendocrine neoplasia: a single-institution series. Eur J Nucl Med Mol Imaging. 2019;46:1902–10.
20. Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. Expert Opin Pharmacother. 2016;17(16):2191–205.
21. Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas. 2012;41(3):461–6.
22. Frojd C, Larsson G, Lampic C, von Essen L. Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study. Health Qual Life Outcomes. 2007;5:18.
23. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. 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: a report from the PROMID Study Group. J Clin Oncol. 2009;27(28):4656–63.
24. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(16):1556–7.
25. Teunissen JJ, Kwekkeboom DJ, Krenning EP. Quality of life in patients with gastroenteropancreatic tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Clin Oncol. 2004;22(13):2724–9.
26. Martini C, Buxbaum S, Rodrigues M, Nilica B, Scarpa L, Holzner B, et al. Quality of life in patients with metastatic gastroenteropancreatic neuroendocrine tumors receiving peptide receptor radionuclide therapy: information from a monitoring program in clinical routine. J Nucl Med. 2018;59(10):1566–73.
27. Marinova M, Mucke M, Mahlberg L, Essler M, Cuhls H, Radbruch L, et al. Improving quality of life in patients with pancreatic neuroendocrine tumor following peptide receptor radionuclide therapy assessed by EORTC QLQ-C30. Eur J Nucl Med Mol Imaging. 2018;45(1):38–46.
28. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med. 2011;52(9):1361–8.
29. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103(2):153–71.
30. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology. 2012;95(2):98–119.
31. Kamp K, Alwani RA, Korpershoek E, Franssen GJ, de Herder WW, Feelders RA. Prevalence and clinical features of the ectopic ACTH syndrome in patients with gastroenteropancreatic and thoracic neuroendocrine tumors. Eur J Endocrinol. 2016;174(3):271–80.
32. Pattison DA, Hicks RJ. Molecular imaging in the investigation of hypoglycaemic syndromes and their management. Endocr Relat Cancer. 2017;24(6):R203–R21.
33. Eldor R, Glaser B, Fraenkel M, Doviner V, Salmon A, Gross DJ. Glucagonoma and the glucagonoma syndrome - cumulative experience with an elusive endocrine tumour. Clin Endocrinol. 2011;74(5):593–8.
34. Grozinsky-Glasberg S, Barak D, Fraenkel M, Walter MA, Mueller-Brand J, Eckstein J, et al. Peptide receptor radioligand therapy is an effective treatment for the long-term stabilization of malignant gastrinomas. Cancer. 2011;117(7):1377–85.
35. Kong G, Callahan J, Hofman MS, Pattison DA, Akhurst T, Michael M, et al. High clinical and morphologic response using (90)Y-DOTA-octreotate sequenced with (177)Lu-DOTA-octreotate induction peptide receptor chemoradionuclide therapy (PRCRT) for bulky

neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2017;44(3):476–89.
36. Perren A, Couvelard A, Scoazec JY, Costa F, Borbath I, Delle Fave G, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. Neuroendocrinology. 2017;105:196–200.
37. Milione M, Maisonneuve P, Spada F, Pellegrinelli A, Spaggiari P, Albarello L, et al. The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories. Neuroendocrinology. 2017;104(1):85–93.
38. Tang LH, Basturk O, Sue JJ, Klimstra DS. A practical approach to the classification of WHO grade 3 (G3) well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. Am J Surg Pathol. 2016;40(9):1192–202.
39. Heetfeld M, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 2015;22(4):657–64.
40. Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer. 2013;20(5):649–57.
41. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013;24(1):152–60.
42.• Thang SP, Lung MS, Kong G, Hofman MS, Callahan J, Michael M, et al. Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN) - a single-institution retrospective analysis. Eur J Nucl Med Mol Imaging. 2018;45(2):262–77
Clinical series showing potential effectiveness of PRRT in Grade 3 NEN particularly for Ki-67 21–55% subgroup.
43. Nicolini S, Severi S, Ianniello A, Sansovini M, Ambrosetti A, Bongiovanni A, et al. Investigation of receptor radionuclide therapy with (177)Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. Eur J Nucl Med Mol Imaging. 2018;45:923–30.
44.• Carlsen EA, Fazio N, Granberg D, Grozinsky-Glasberg S, Ahmadzadehfar H, Grana CM, et al. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. Endocr Relat Cancer. 2019;26(2):227–3.
More recent multicenter cohort study reporting favorable efficacy of PRRT in patients with G3 NEN.
45. Hofman MS, Hicks RJ. Peptide receptor radionuclide therapy for neuroendocrine tumours: standardized and randomized, or personalized? Eur J Nucl Med Mol Imaging. 2014;41(2):211–3.
46. de Jong M, Breeman WA, Valkema R, Bernard BF, Krenning EP. Combination radionuclide therapy using 177Lu- and 90Y-labeled somatostatin analogs. J Nucl Med. 2005;46(Suppl 1):13S–7S.
47. Villard L, Romer A, Marincek N, Brunner P, Koller MT, Schindler C, et al. Cohort study of somatostatin-based radiopeptide therapy with [(90)Y-DOTA]-TOC versus [(90)Y-DOTA]-TOC plus [(177)Lu-DOTA]-TOC in neuroendocrine cancers. J Clin Oncol. 2012;30(10):1100–6.
48. Dumont RA, Seiler D, Marincek N, Brunner P, Radojewski P, Rochlitz C, et al. Survival after somatostatin based radiopeptide therapy with (90)Y-DOTATOC vs. (90)Y-DOTATOC plus (177)Lu-DOTATOC in metastasized gastrinoma. Am J Nucl Med Mol Imaging. 2015;5(1):46–55.
49. McStay MK, Maudgil D, Williams M, Tibballs JM, Watkinson AF, Caplin ME, et al. Large-volume liver metastases from neuroendocrine tumors: hepatic intraarterial 90Y-DOTA-lanreotide as effective palliative therapy. Radiology. 2005;237(2):718–26.
50. Pool SE, Kam BL, Koning GA, Konijnenberg M, Ten Hagen TL, Breeman WA, et al. [(111)In-DTPA]octreotide tumor uptake in GEPNET liver metastases after intra-arterial administration: an overview of preclinical and clinical observations and implications for tumor radiation dose after peptide radionuclide therapy. Cancer Biother Radiopharm. 2014;29(4):179–87.
51. Beauregard JM, Hofman MS, Kong G, Hicks RJ. The tumour sink effect on the biodistribution of 68Ga-DOTA-octreotate: implications for peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging. 2012;39(1):50–6.
52. Hicks RJ, Jackson P, Kong G, Ware RE, Hofman MS, Pattison DA, et al. First-in-human trial of (64)Cu-SARTATE PET imaging of patients with neuroendocrine tumours demonstrates high tumor uptake and retention, potentially allowing prospective dosimetry for peptide receptor radionuclide therapy. J Nucl Med. 2019;60(6):777–85.
53. van Essen M, Krenning EP, Kam BL, de Herder WW, van Aken MO, Kwekkeboom DJ. Report on short-term side effects of treatments with 177Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2008;35(4):743–8.
54. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide 177Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2011;38(2):302–11.

55. Hubble D, Kong G, Michael M, Johnson V, Ramdave S, Hicks RJ. 177Lu-octreotate, alone or with radiosensitising chemotherapy, is safe in neuroendocrine tumour patients previously treated with high-activity 111In-octreotide. Eur J Nucl Med Mol Imaging. 2010;37(10):1869–75.
56. Kong G, Thompson M, Collins M, Herschtal A, Hofman MS, Johnston V, et al. Assessment of predictors of response and long-term survival of patients with neuroendocrine tumour treated with peptide receptor chemoradionuclide therapy (PRCRT). Eur J Nucl Med Mol Imaging. 2014;41(10):1831–44.
57. Claringbold PG, Turner JH. Pancreatic neuroendocrine tumor control: durable objective response to combination 177Lu-octreotate-capecitabine-temozolomide radiopeptide chemotherapy. Neuroendocrinology. 2016;103(5):432–9.
58. Nonnekens J, van Kranenburg M, Beerens CE, Suker M, Doukas M, van Eijck CH, et al. Potentiation of peptide receptor radionuclide therapy by the PARP inhibitor olaparib. Theranostics. 2016;6(11):1821–32.
59. Wild D, Fani M, Fischer R, Del Pozzo L, Kaul F, Krebs S, et al. Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. J Nucl Med. 2014;55(8):1248–52.
60.• Navalkissoor S, Grossman A. Targeted alpha particle therapy for neuroendocrine tumours: the next generation of peptide receptor radionuclide therapy. Neuroendocrinology. 2019;108(3):256–6.

Review article providing a summary and comprehensive review of current status of Alpha Therapy for NEN.

61. Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, et al. 225Ac-PSMA-617 for PSMA-targeted alpha-radiation therapy of metastatic castration-resistant prostate cancer. J Nucl Med. 2016;57(12):1941–4.
62. Sathekge M, Knoesen O, Meckel M, Modiselle M, Vorster M, Marx S. (213)Bi-PSMA-617 targeted alpha-radionuclide therapy in metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2017;44(6):1099–100.
63. Kratochwil C, Giesel FL, Bruchertseifer F, Mier W, Apostolidis C, Boll R, et al. (2)(1)(3)Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol Imaging. 2014;41(11):2106–19.
64. Nayak TK, Norenberg JP, Anderson TL, Prossnitz ER, Stabin MG, Atcher RW. Somatostatin-receptor-targeted alpha-emitting 213Bi is therapeutically more effective than beta(−)-emitting 177Lu in human pancreatic adenocarcinoma cells. Nucl Med Biol. 2007;34(2):185–93.
65. Muller C, Domnanich KA, Umbricht CA, van der Meulen NP. Scandium and terbium radionuclides for radiotheranostics: current state of development towards clinical application. Br J Radiol. 2018;91(1091):20180074.
66. Roosenburg S, Laverman P, van Delft FL, Boerman OC. Radiolabeled CCK/gastrin peptides for imaging and therapy of CCK2 receptor-expressing tumors. Amino Acids. 2011;41(5):1049–58.
67. Gotthardt M, Béhé MP, Grass J, Bauhofer A, Rinke A, Schipper ML, et al. Added value of gastrin receptor scintigraphy in comparison to somatostatin receptor scintigraphy in patients with carcinoids and other neuroendocrine tumours. Endocr Relat Cancer. 2006;13(4):1203–11.
68. Reubi JC, Schaer J-C, Waser B. Cholecystokinin(CCK)-A and CCK-B/gastrin receptors in human tumors. Cancer Res. 1997;57(7):1377–86.
69. Béhé M, Behr TM. Cholecystokinin-B (CCK-B)/gastrin receptor targeting peptides for staging and therapy of medullary thyroid cancer and other CCK-B receptor expressing malignancies. Pept Sci. 2002;66(6):399–418.
70. Körner M, Waser B, Reubi JC, Miller LJ. CCK(2) receptor splice variant with intron 4 retention in human gastrointestinal and lung tumours. J Cell Mol Med. 2010;14(4):933–43.
71. Zovato S, Kumanova A, Dematte S, Sansovini M, Bodei L, Di Sarra D, et al. Peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE in individuals with neck or mediastinal paraganglioma (PGL). Horm Metab Res. 2012;44(5):411–4.
72. Forrer F, Riedweg I, Maecke HR, Mueller-Brand J. Radiolabeled DOTATOC in patients with advanced paraganglioma and pheochromocytoma. Q J Nucl Med Mol Imaging. 2008;52(4):334–40.
73. Pinato DJ, Black JR, Ramaswami R, Tan TM, Adjogatse D, Sharma R. Peptide receptor radionuclide therapy for metastatic paragangliomas. Med Oncol. 2016;33(5):47.
74. Puranik AD, Kulkarni HR, Singh A, Baum RP. Peptide receptor radionuclide therapy with (90)Y/ (177)Lu-labelled peptides for inoperable head and neck paragangliomas (glomus tumours). Eur J Nucl Med Mol Imaging. 2015;42(8):1223–30.
75. van Essen M, Krenning EP, Kooij PP, Bakker WH, Feelders RA, de Herder WW, et al. Effects of therapy with [177Lu-DOTA0, Tyr3]octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. J Nucl Med. 2006;47(10):1599–606.
76. Kong G, Grozinsky-Glasberg S, Hofman MS, Callahan J, Meirovitz A, Maimon O, et al. Efficacy of peptide receptor radionuclide therapy for functional metastatic paraganglioma and pheochromocytoma. J Clin Endocrinol Metab. 2017;102(9):3278–87.
77. Kroiss A, Putzer D, Uprimny C, Decristoforo C, Gabriel M, Santner W, et al. Functional imaging in phaeochromocytoma and neuroblastoma with (68)Ga-DOTA-Tyr (3)-octreotide positron emission

tomography and (123)I-metaiodobenzylguanidine. Eur J Nucl Med Mol Imaging. 2011;38(5):865–73.
78. Gains JE, Bomanji JB, Fersht NL, Sullivan T, D'Souza D, Sullivan KP, et al. 177Lu-DOTATATE molecular radiotherapy for childhood neuroblastoma. J Nucl Med. 2011;52(7):1041–7.
79. Kong G, Hofman MS, Murray WK, Wilson S, Wood P, Downie P, et al. Initial experience with gallium-68 DOTA-octreotate PET/CT and peptide receptor radionuclide therapy for pediatric patients with refractory metastatic neuroblastoma. J Pediatr Hematol Oncol. 2016;38(2):87–96.
80. Lewin J, Cullinane C, Akhurst T, Waldeck K, Watkins DN, Rao A, et al. Peptide receptor chemoradionuclide therapy in small cell carcinoma: from bench to bedside. Eur J Nucl Med Mol Imaging. 2015;42(1):25–32.

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