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Review Article

# Meeting Notes of the Taiwan Neuroendocrine Tumor Society & Taiwan Society of Nuclear Medicine Joint Conference - Peptide Receptor Radionuclide Therapy Targeting for Gastroenteropancreatic Neuroendocrine Tumors: Basic Principles and State-of-the-art Clinical Practice

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## Abstract

**Objective:** The current study aimed to investigate the basic principles and clinical applications, including the selection of proper candidates, follow-up strategies, and radiation protection issues relating to peptide receptor radionuclide therapy (PRRT). **Data Sources and Study Selection:** We searched various scientific databases using specific keywords. **Results:** Due to the overexpression of somatostatin receptors in neuroendocrine tumors (NETs), PRRT is currently considered an important therapeutic modality for the management of NETs. **Conclusion:** PRRT incorporates the systemic administration of a tumor-targeting radiolabeled peptide to patients with tumors, allowing for more precise delivery of radiation doses to tumor sites while sparing normal tissues.

**Keywords:** Gastroenteropancreatic neuroendocrine tumors, peptide receptor radionuclide therapy

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## Introduction

### What is peptide receptor radionuclide therapy?

The work of Paul Ehrlich, a physician-scientist and Nobelist, led to the development of chemotherapy and specific targeted treatment concepts. Ehrlich formulated the "side-chain theory," which extended to the receptor-ligand concept, and proposed creating specific drugs, so-called "magic bullets," that could kill microbes or target cells but spare healthy tissues.[1,2] Targeted radionuclide therapy (TRNT) is a type of targeted therapy that uses the systemic administration of radiolabeled drugs that target specific molecular alterations expressed or upregulated in tumor cells. The radiolabeled drugs contain high energy β or α particles with a shorter particle range, which cause double-strand DNA damage both directly and indirectly via water radiolysis in tumor sites while sparing nonexpressing normal tissues.[3,4] Because β particles have a long radiation range within tissues (0.05–12 mm), neighboring cells that are not specifically targeted by the radioconjugate are also eradicated by the radiation (cross-fire effect). This effect is considered ideal for targeting large tumors with a heterogeneous target distribution.[5]

The current common radionuclides used in radiotherapy include $^{177}$Lu, $^{90}$Y, $^{131}$I, and $^{225}$Ac. The commission of β and gamma photons by $^{177}$Lu and $^{131}$I can be used for both diagnosis imaging and therapy with the same or related radiopharmaceuticals (theranostics or theragnostics), and also in posttreatment imaging to verify radiation delivery.[6] This theranostic principle can be applied in precision oncology, described as "see what we treat and treat what we see" by Dr. Richard Baum.[7] Hence, patients with advanced tumors can be selected properly and treated effectively with reduced toxicity.[8]

Peptide receptor radionuclide therapy (PRRT) is a type of TRNT which involves the systemic delivery of radiolabeled peptides that can bind specific peptide receptors expressed in higher densities on tumor cell membranes than in nontumor tissues, leading to tumor-specific binding and destruction.[5] As somatostatin receptors (SSTRs) tend to be overexpressed in neuroendocrine tumors (NETs), an antagonist at the SSTR has been introduced as a theranostic pair for NETs,[9] and the efficacy of PRRT has been evaluated over the last 25 years. The landmark NETTER-1 study showed promising results with beneficial effects on objective response, quality of life, progression-free survival (PFS), and a clear trend toward an overall survival (OS) benefit in patients with NETs treated by PRRT with $^{177}$Lu-DOTATATE ($^{177}$Lu-DOTA-Tyr$^3$-octreotate) compared with high doses of octreotide alone.[10,11] Based on randomized data from the NETTER-1 trial, $^{177}$Lu-DOTATATE was then approved by the US Food and Drug Administration for the treatment of SSTR-positive gastroenteropancreatic (GEP) NETs, including foregut, midgut, and hindgut NETs in adults.[12] The two peptides most commonly used for PRRT are DOTATOC and DOTATATE,[12] while $^{177}$Lu-DOTATATE is the only authorized peptide in the US and Europe, and it was also authorized in Taiwan in July 2021. With continuous evolution, PRRT can be of great clinical value for patients with cancers, and theranostic pairs can be combined to shape the future of precision radiation oncology.

## Data Sources and Study Selection

We searched Medline, PubMed, and Google Scholar electronic databases using the following keywords to identify relevant articles: neuroendocrine neoplasms (NENs), NETs, GEP-NETs, TRNT, PPRT, and prognosis, and/or survival. Only articles published in English were selected. Due to the heterogeneity of the currently available data, we systematized the current review using specific topics: (1) The indications of PRRT in GEP-NETs, (2) The safety of PRRT, and (3) The follow-up strategy for NET patients treated with PRRT.

## Indications of Peptide Receptor Radionuclide Therapy in Gastroenteropancreatic-neuroendocrine Tumors

NENs are divided into well-differentiated NETs and poorly differentiated neuroendocrine carcinomas (NECs) based on molecular differences, and they can occur in multiple sites throughout the body.[13] NETs are relatively rare; however, the reported incidence has gradually increased in Western populations,[14,15] with a similar trend seen in Taiwan.[16] GEP-NETs account for about two-thirds of all NETs. The treatment for inoperable advanced GEP-NETs has evolved in recent years. The landmark PROMID study[17] demonstrated both the antisecretory and antitumor efficacy of somatostatin analogs (SSAs), and octreotide and lanreotide remain first-line management and therapy for functional and nonfunctional NETs.[9] Due to the pivotal role of SSAs in NET biology, PRRT, which uses SSA-labeled radionuclides, can potentially target primary as well as metastatic GEP-NETs.[15]

PRRT has become an established treatment method for advanced/metastatic midgut NETs following the publication of the NETTER-1 study, the first prospective and randomized phase 3 trial involving PRRT by the Rotterdam group. In the NETTER-1 study, a total of 229 patients with well-differentiated advanced, progressive, somatostatin-receptor-positive midgut NETs were randomized to receive $^{177}$Lu-DOTATATE 7.4 GBq every 8 weeks and four intravenous infusions in association with octreotide long-acting repeatable (LAR) 30 mg (116 patients, $^{177}$Lu-DOTATATE group), or octreotide LAR 60 mg alone every 4 weeks (113 patients, control group). The primary objective of the trial was met in 2017, showing a significantly longer PFS at month 20 in the $^{177}$Lu-DOTATATE group (65.2%, 95% confidence interval [CI], 50.0–76.8) than the control group (10.8%, 95% CI: 3.5–23.0, $P < 0.001$). Lu-DOTATATE was also associated with a higher objective response rate (18% vs. 3%) at 3 months after the fourth PRRT cycle.[10] In the final analysis, $^{177}$Lu-DOTATATE was associated with more favorable, albeit not statistically significant, OS

at any time point of follow-up, and a longer increase in the median OS of 11.7 months with $^{177}$Lu-DOTATATE versus high-dose long-acting octreotide (48.0 vs. 36.3 months) could be considered clinically relevant.[18] Although results from randomized control trials of PRRT in pancreatic NETs (PNETs) are lacking, the recent NETTER-R study used retrospective real-world data of $^{177}$Lu-DOTATATE treatment in patients with progressive, advanced PNETs, and reported the effects of treatment on PFS (median: 24.8 months) and the objective response rate (40.3%), which reinforced the role of $^{177}$Lu-DOTATATE in patients with PNETs.[19] The Rotterdam protocol is now one of the most commonly used therapy regimens.

PRRT is considered an option for the treatment of recurrent, locoregional advanced and/or distant metastatic GEP-NETs following progression on SSAs by current evidence-based international guidelines. PRRT has also been recommended as third-line treatment and beyond for PNETs following progression on SSAs or target agents (everolimus and/or sunitinib) [Table 1]. The key factor for eligibility is a lesion demonstrating adequate SSTR expression detected by SSTR-positron emission tomography/computed tomography (PET/CT) or SSTR-PET/magnetic resonance imaging (MRI).[12,20-22] PRRT may be considered for symptom control in progressive disease or functional PNET, according to the European Society for Medical Oncology.[12] For high-grade (WHO G3) NETs, published data from retrospective studies support the therapeutic consideration of PRRT in G3 NETs, but the use of PRRT for NECs with high Ki-67 is less defined.[12] Prospective trials, including NETTER-2 (NCT03972488) and COMPOSE (NCT04919226) incorporating patients with G3 NETs, are currently ongoing.

## Safety of Peptide Receptor Radionuclide Therapy

Despite high and specific tumor uptake with PRRT, physiological distribution of $^{177}$Lu can result in toxicity. Because the radiotracer is excreted through the renal pathway and irreversible renal reabsorption of the radiolabeled peptides occurs mainly in the proximal tubules, the kidneys are considered critical organs for radiation toxicity. Currently, the administration of a mixture of the basic amino acids lysine and arginine before and following radiopeptide infusion to competitively inhibit its absorption is the most widely used strategy to minimize renal radiation effects, and can lower long-term renal toxicity (<2%).[23] Overall, end-stage renal disease as a consequence of PRRT is extremely rare.[24]

In the NETTER-1 study, most patients showed only moderate toxicity and the discontinuation rate due to PRRT-related toxicity was 5%. Acute side effects include nausea, vomiting, fatigue, and abdominal pain, which are mainly caused by the simultaneous infusion of amino acids.[10] Subacute effects include carcinoid crisis and myelosuppression. A minority of patients (1%) may develop carcinoid crisis, which usually occurs within 48 h of the first infusion and is related to the massive release of active amines. PRRT-induced myelosuppression is usually G1-2 at 4–6 weeks after infusion and has a transient nature. Opportunistic infections are not observed in patients with lymphopenia. The overall incidence is acceptable (≤5%). Myelodysplastic syndrome or acute leukemia is a rare delayed side effect with long-term risk reported in roughly 2%–3% of patients at a median of 2 years after therapy.[25,26]

Radiopharmaceutical therapy is not recommended during pregnancy and should be delayed until after delivery or pregnancy termination. Breastfeeding should be halted during treatment and not resumed until 2.5 months posttreatment. It is safe to breastfeed future children. Contraceptive use is advised for 6 months after the final treatment.[26]

## Radionuclide and Essential Radiation Protection for Peptide Receptor Radionuclide Therapy

$^{177}$Lu emits not only β particles but also two γ emissions, which present an external radiation hazard to those in contact with the patient.[27] Biological excretion of the radiopharmaceutical is another possible safety hazard. Considering comparatively lower γ emission energies and the relative abundance and fewer routes of biological excretion compared to $^{131}$I, which has been safely administered for hyperthyroidism on an outpatient basis for many years, $^{177}$Lu is regarded as a favorable treatment for minimizing public radiation exposure.

**Table 1: Peptide receptor radionuclide therapy recommendations by international practice guidelines**

| | NCCN-2021 | ESMO-2020 | ENETS-2016 |
|---|---|---|---|
| WHO Grade 1/2 gastrointestinal NET | Symptomatic, high tumor burden or progressed disease<br>SSTR imaging (+)<br>Progression on SSA (2nd line) | SSTR imaging (+)<br>Progression on SSA or everolimus (2nd line) | Carcinoid syndrome or NF: SSTR imaging (+), progression on SSA (2nd line) |
| WHO Grade 1/2 PNET | Symptomatic, high tumor burden or progressed disease<br>SSTR imaging (+)<br>Progression on SSA (2nd line) or everolimus or sunitinib (3rd or beyond) | Grade 1 or slow growth: Progression on SSA and everolimus/sunitinib/chemotherapy (3rd or beyond)<br>Grade 2: Progression on everolimus/sunitinib/chemotherapy (2nd or 3rd line) | Functional: SSTR imaging (+), progression on SSA or everolimus (2nd or 3rd line)<br>Nonfunctional: SSTR imaging (+), progression on SSA or everolimus/sunitinib or chemotherapy (3rd or beyond) |

NET: Neuroendocrine tumors, PNET: Pancreatic NET, NF-PNET: Nonfunctioning pancreatic NETs, ENETS: European NET Society, CSNET: Chinese Study Group for NETs, NANSETS: North American NET Society, NCCN: National Comprehensive Cancer Network, WHO: World Health Organization, SSTR: Somatostatin receptor, SSA: Somatostatin analog, ESMO: European Society for Medical Oncology

$^{177}$Lu has a physical half-life of 6.7 days,[26] which increases the possibility of prolonged contamination. Blood and urine are the main sources of contamination during and after radionuclide administration. Very rapid blood clearance is observed in the first 1–2 h of treatment,[23] while the mean terminal blood half-life is 71 ± 28 h.[26] Therefore, medical staff should be advised to take universal precautions and to collect the smallest amount of body fluid necessary for testing within the first 3 days after PRRT.[26] Because the primary route of excretion of $^{177}$Lu-DOTATATE is through the kidneys, with a cumulative excretion of 44% within 5 h, 58% within 24 h, and 65% within 48 h after administration, preventing urinary contamination is the main issue for patients for the first 3 days after therapy.[26] In addition, during the production process of $^{177}$Lu by neutron activation, $^{177m}$Lu is also produced. $^{177m}$Lu has a half-life of 160 days, and therefore, it is important to survey and handle laboratory and clinical waste (including urine, feces, and emesis) containing $^{177m}$Lu appropriately before disposal from the treatment center.[26,28]

Dialysis patients can be treated with a reduced dose, and dialysis should be delayed 24 h after treatment in consideration of the decreased drug-clearance rate in these patients.[29] Radiopharmaceutical therapy is almost invariably contraindicated during pregnancy, and 6 months of contraception should be used following the end of treatment. Delay autopsy or cremation of deceased patients after 3 months is recommended.[26]

## The Follow-up Strategy for Neuroendocrine Tumor Patients Treated With Peptide Receptor Radionuclide Therapy

The North American NET Society and the Society of Nuclear Medicine and Molecular Imaging recommend clinical evaluation and laboratory and imaging tests to monitor patients after PRRT. Clinical evaluation, laboratory tests, and diagnostic imaging to assess symptoms and posttreatment sequelae should ideally be conducted in the 1$^{st}$ month and every 3 months within the 1$^{st}$ year after PRRT.[26] There are no formal recommendations for tracking tumor markers after PRRT. The NCCN NET guidelines recommend tracking markers, if clinically applicable, every 3–12 months.[21]

Imaging is essential in staging, treatment selection, response assessment, and follow-up of PRRT. Combining morphological imaging (CT or MRI) and functional imaging (SSTR PET/CT, such as 68Ga-DOTATOC) can optimize response assessments and increase sensitivity and specificity.[30] Nearly 10% of patients with stable disease may show the pseudoprogression of metastatic lesions during the first cycle of treatment, probably due to edema from radiation to the tumor.[26]

Recently, Bodei *et al*. developed a PRRT predictive quotient (PPQ) that integrated blood-derived NET-specific gene transcript expression and tumor grade by tissue Ki67 values, and showed that PPQ is a highly specific predictor of the efficacy of PRRT with an accuracy of 95%.[31] The same study group found concordance between disease status, PPQ and NETest, which is a 51 multigene assay based on PCR analysis of specific NET circulating transcripts. The authors proposed that PPQ can serve as a good predictive biomarker, and that the NETest is a good response biomarker of PRRT.[32]

## Conclusion

PRRT incorporates the systemic administration of a tumor-targeting radiolabeled peptide to patients with SSTRs expressing NENs. PRRT based on $^{177}$Lu-DOTATATE is an effective treatment for patients with advanced, well-differentiated GEP-NETs, and has a favorable long-term safety profile. This review provides information on the basic principles, state-of-the-art clinical practice, and radiation protection strategies for the application of this novel treatment.

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### Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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### Conflicts of interest

There are no conflicts of interest.

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