Peptide receptor radionuclide therapy (PRRT) special issue

Shaunak Navalkissoor [1,*], Robert P Millar [2, 3]

[1] Department of Nuclear Medicine and Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free London NHS Foundation Trust, London, UK.

[2] Centre for Neuroendocrinology, University of Pretoria, Pretoria, South Africa.

[3] Department of Integrative Biomedical Sciences, Faculty of Health Sciences, Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa.

*Correspondence: Shaunak Navalkissoor, Department of Nuclear Medicine and Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free London NHS Foundation Trust, London, UK. Email: s.navalkissoor@nhs.net

Peptide receptor radionuclide therapy (PRRT), a form of radioligand therapy (RLT), is a well-established treatment in well-differentiated neuroendocrine tumour (NET), but RLT is being increasingly employed in other cancers such as prostatic cancer. PRRT is a type of molecular radiotherapy and uses the theranostics principle, where the same target molecule utilises different radionuclides for imaging and therapy. The imaging of this target molecule first identifies whether the tumour exhibits enough of the diagnostic radionuclide to indicate adequate concentration of the therapeutic radionuclide pair (beta or alpha or auger emitting radionuclide pair). In NETs, the target molecule is predominantly the somatostatin receptor (SSR). This special issue of the journal focuses predominantly on PRRT in NETs but also touches on current and potential utilisation in other cancers.

PRRT was first administered in a NET patient (using auger electron high-dose ^{111}In-pentetreotide) at the Erasmus Medical Centre in 1992.[1] Subsequently, there has been significant development with new radionuclides and new peptides. PRRT has become more widely employed since the *European Marketing Authority* (EMA) and *Food and Drug Administration* (FDA) approved ^{177}Lu-DOTATATE in 2017 and 2018, respectively.[2] Since these approvals, there has been an even greater interest in PRRT in NETs with 798 PubMed hits with search terms 'PRRT' in the past 5 years (2020–2024).[3] This special issue explores the current evidence and emerging developments of PRRT. A figure depicting the mechanism of action of PRRT is shown in Figure 1.

In the special issue, Kuiper and colleagues give an excellent overview of the status, clinical practice and treatment options for patients with grade 1 and 2 GEPNETs.[4] They review the efficacy of ^{177}Lu-DOTATATE and discuss the proposed use of PRRT in current guidelines. Next, Parghane and colleagues evaluate the side effects of PRRT and discuss the main concerns of PRRT, viz. the long-term renal and bone marrow toxicity.[5] Furthermore, they provide insights into predicting, preventing and treating PRRT toxicity.

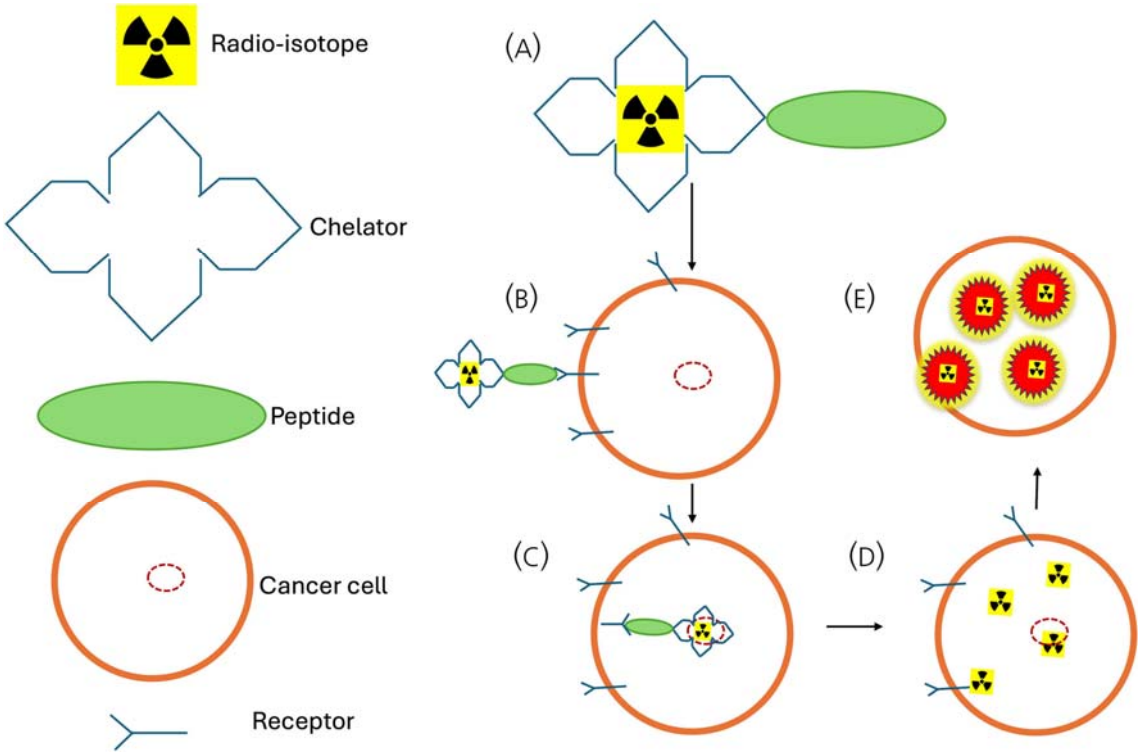

FIGURE 1. PRRT consists of a therapeutic radionuclide (e.g. ^{177}Lu, ^{90}Y), a cyclic somatostatin analogue (e.g. Tyr3-octreotide or Tyr3-octreotate), bound together by a chelator (e.g. DOTA). On infusion of the radiolabelled somatostatin analogue, the molecule (A) binds to the somatostatin receptor on the NET cell surface (B) and becomes internalised by receptor-mediated endocytosis (C). Accumulation of other PRRT molecules in the cell is shown (D), with the irradiation of the tumour cell (E) resulting in tumour damage and death.

Following on from this, Sorbye and colleagues have published on the application of PRRT in G3 NETs.[6] This is a timely review as the NETTER-2 study recently published a positive study in the NET G3 subgroup, demonstrating major PFS superiority of PRRT versus high-dose somatostatin analogues (SSA) as first-line treatment for the NET G3 subgroup.[4] Although limited data are available, they also provide findings, indicating that PRRT may be of value for NEC, as histological distinction between NEC and NET G3 can be difficult when Ki-67 is below 55%. They suggest PRRT may be of value in refractory NEC, in which there is high SSR expression, an absence of rapid progression and Ki-67 below 55%.

PRRT patients are preselected based on the demonstration of sufficient SSR. However, this may not be sufficient to predict outcomes. The article by Kong and colleagues[7] explores the use of anatomical, molecular imaging and peptide biomarkers, as well as novel biomarkers to evaluate responses to treatment. Although anatomical imaging remains the most common method to assess response, SSR PET/CT may be valuable in patients with disease that is better seen on SSR PET. Liquid biomarkers, although not currently widely available, may also have an important role in assessing response to PRRT. Di Franco and colleagues evaluate the role of dual PET (FDG and SSR PET) in the evaluation of tumour heterogeneity and better selection of patients for PRRT.[8] They show that FDG can outperform WHO grading in predicting outcomes and can be useful for patient selection for PRRT, capturing patients with tumour heterogeneity. In addition, Dr. Prasad and colleagues presented an ENETS theranostics Task

Force report on the Challenges in Developing Response Evaluation Criteria for Peptide Receptor Radionuclide Therapy.[9]

There are various mechanisms that have been used to optimise PRRT, which are explored in this special issue. Chan and colleagues review the value of combining chemotherapy with PRRT (PRCRT) to optimise the radiosensitising potential.[10] PRCRT results in higher disease control rates and progression-free survival (PFS), but there is a possible higher incidence of treatment-related myeloid neoplasms vs. PRRT alone. Navalkissoor and colleagues evaluate the early promising results on the potential next generation of PRRT (targeted alpha therapy), which appears to result in higher partial or complete responses vs. beta-emitting PRRT.[11] Puranik and colleagues explore new imaging and therapeutic radiopharmaceuticals that are being developed to optimise the effectiveness of PRRT.[12]

In addition to GEP-NETs, PRRT has also been shown to be useful in other SSR-expressing tumours, for example phaeochromocytoma, paragangliomas and bronchial NETs. Santo and colleagues discuss the evidence for PRRT in currently unlicensed indications.[13] PRRT has also been used in the neoadjuvant setting. Kashyap and colleagues evaluate the value of PRRT to downstage tumours as a bridge to surgery.[14]

The special feature also includes excellent research papers. The first of these is from Padwal and colleagues, who present work on a peripheral blood RNA-based biomarker.[15] They report work on the development of a multi-gene NETseq ensemble classifier using peripheral blood RNA-Seq. In this study, they show the potential role of this novel biomarker in early treatment response monitoring of PRRT. Kleynhans and colleagues describe the synthesis and characterisation of DOTA-Kisspeptin-10 as a potential pan-tumour radiopharmaceutical.[16] Their study highlights the huge potential of utilising the vast number of physiological/pathophysiological peptides that have yet to be explored. Papantoniou and colleagues present their work on hypalbuminaemia predicting outcomes in PRRT.[17] They found that albumin was the single best prognosticator in predicting overall survival in patients treated with PRRT. Trikalinos and colleagues reviewed the literature for the use of PRRT in patients with end-stage renal failure; they found that patients undergoing haemodialysis can be considered for PRRT with dose adjustment under close observation.[18]

We extend our sincere gratitude to our distinguished colleagues for their contributions to this special feature on PRRT. It has been a pleasure collaborating to deliver a comprehensive overview of these complex topics. Through publishing this special issue on PRRT in the Journal of Neuroendocrinology, we anticipate that the journal will become a repository for submissions in PRRT.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES

1. 1Levine R, Krenning EP. Clinical history of the Theranostic radionuclide approach to neuroendocrine tumors and other types of cancer: historical review based on an interview of Eric P. Krenning by Rachel Levine. *J Nucl Med*. 2017; 58(Suppl 2): 3S-9S.

2. Hennrich U, Kopka K. Lutathera(®): the first FDA-and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy. *Pharmaceuticals Basel*. 2019; 12(3): 114.
3. https://pubmed.ncbi.nlm.nih.gov/?term=prrt&filter=dates.2020%2F1%2F1-2024%2F12%2F31&sort=date Search Term "PRRT" 16.01.2025.
4. Kuiper J, Zoetelief E, Brabander T, de Herder WW, Hofland J. Current status of peptide receptor radionuclide therapy in grade 1 and 2 gastroenteropancreatic neuroendocrine tumours. *J Neuroendocrinol*. 2025; 37(3):e13469. doi:10.1111/jne.13469
5. Parghane RV, Basu S. Toxicity manifestations encountered in peptide receptor radionuclide therapy setting. *J Neuroendocrinol*. 2025; 37(3):e13464. doi:10.1111/jne.13464
6. Sorbye H, Kong G, Grozinsky-Glasberg S, Strosberg J. PRRT in high-grade digestive neuroendocrine neoplasms (NET G3 and NEC). *J Neuroendocrinol*. 2025; 37(3):e13443. doi:10.1111/jne.13443
7. Kong G, Noe G, Chiang C, Herrmann K, Hope TA, Michael M. Assessment of response to PRRT including anatomical and molecular imaging as well as novel biomarkers. *J Neuroendocrinol*. 2025; 37(3):e13461. doi:10.1111/jne.13461
8. Di Franco M, Fortunati E, Zanoni L, Fanti S, Ambrosini V. The role of combined FDG and SST PET/CT in neuroendocrine tumors. *J Neuroendocrinol*. 2025; 37(3):e13474. doi:10.1111/jne.13474
9. Prasad V, Koumarianou A, Denecke T, et al. Challenges in developing response evaluation criteria for peptide receptor radionuclide therapy: a consensus report from the European neuroendocrine tumor society advisory board meeting 2022 and the ENETS Theranostics task force. *J Neuroendocrinol*. 2025; 37(2):e13479. doi:10.1111/jne.13479
10. Chan DS, Kanagaratnam AL, Pavlakis N, Chan DL. Peptide receptor chemoradionuclide therapy for neuroendocrine neoplasms: a systematic review. *J Neuroendocrinol*. 2025; 37(3):e13355. doi:10.1111/jne.13355
11. Navalkissoor S, Grossman A. Somatostatin receptor-linked α-particle therapy in neuroendocrine tumours. *J Neuroendocrinol*. 2025; 37(3):e13463. doi:10.1111/jne.13463
12. Puranik AD, Dev ID, Prasad V. Frontiers in radiopharmaceuticals for neuroendocrine tumors. *J Neuroendocrinol*. 2025; 37(3):e70006.
13. Santo G, di Santo G, Cicone F, Virgolini I. Peptide receptor radionuclide therapy with somatostatin analogues beyond GEPNETs. *J Neuroendocrinol*. 2025; 37(3):e70013.
14. Kashyap R, Raja S, Adusumilli A, et al. Role of neoadjuvant peptide receptor radionuclide therapy in unresectable and metastatic gastro-entero-pancreatic neuroendocrine neoplasms: a scoping review. *J Neuroendocrinol*. 2025; 37(3):e13425. doi:10.1111/jne.13425
15. A-seq based NETseq ensemble classifier: a potential novel tool for non-invasive detection and treatment response assessment in neuroendocrine tumor patients receiving 177Lu-DOTATATE PRRT. *J Neuroendocrinol*. 2025; 37(3):e13469. doi:10.1111/jne.13462
16. Kleynhans J, Reeve R, Driver CHS, et al. Synthesis and characterisation of DOTA-kisspeptin-10 as a potential gallium-68/lutetium-177 pan-tumour radiopharmaceutical. *J Neuroendocrinol*. 2025; 37(3):e13487. doi:10.1111/jne.13487
17. Papantoniou D, Frösss-Baron K, Garske-Román U, et al. Hypoalbuminemia, but not derived neutrophil to lymphocyte ratio (dNLR), predicts overall survival in neuroendocrine tumours undergoing peptide receptor radionuclide therapy: a

retrospective, cohort study of 557 patients. *J Neuroendocrinol*. 2025; 37(3):e13379. doi:10.1111/jne.13379
18. Trikalinos NA, Kim H, Vijayan A, Amurao M, Prasad V. Use of approved Lu-177 radiopharmaceuticals in patients with end-stage renal disease: a review of the literature and proposed treatment algorithm. *J Neuroendocrinol*. 2024; 36(6):e13393. doi:10.1111/jne.13393