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INVITED REVIEW

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Assessment of response to PRRT including anatomical and molecular imaging as well as novel biomarkers

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Abstract

Peptide receptor radionuclide therapy (PRRT) is an effective treatment for both oncological and hormone control and is a widely accepted standard of care treatment for patients with neuroendocrine neoplasms (NEN). Its use is anticipated to increase significantly, and this demands accurate tools and paradigms to assess treatment response post PRRT. This article outlines the current role and future developments of anatomical, molecular imaging and biomarkers for response assessment to PRRT, highlighting the challenges and provides perspectives for the need to focus on a multimodality, multidisciplinary and individualised approach for patients with this complex heterogeneous disease.

KEYWORDS
biomarkers, molecular imaging, PRRT, radiology, response

1 | INTRODUCTION

Neuroendocrine neoplasms (NEN) represent a diverse group of uncommon cancers arising from the diffuse endocrine system, most typically from gastroenteropancreatic (GEP) origins, and also from the bronchopulmonary system or thymus.[1] NEN often produce symptoms due to tumour growth, visceral/vascular obstruction or inappropriate hormone hypersecretion, resulting in debilitating diarrhoea, nausea, flushing and pain; all of which have an impact on patients' quality of life and function. In the setting of metastatic disease, systemic therapies are required. Peptide receptor radionuclide therapy (PRRT) is an effective treatment for both oncological, and hormone and symptoms control. [^{177}Lu]Lu-DOTA-Octreotate is now considered standard of care for patients with somatostatin receptor (SSTR) positive metastatic well-differentiated GEP NEN based on the NETTER-1 trial and multiple prior institutional series.[2,3] There is also increasing

prospective evidence that it is more effective compared to other treatments including sunitinib (*OCCLURANDOM*)[4] and high-dose SSA (*NETTER-2*).[5] Other comparative trials are ongoing (*COMPETE* NCT03049189 and *COMPOSE* NCT04919226), and for other SSTR-expressing malignancies including paraganglioma and pheochromocytoma (NCT04711135, NCT03206060). Many other PRRT trials are in progress, concepts include evaluating dosimetry with PRRT, combination treatments, and the use of new targets or radionuclides (^{225}Ac, ^{212}Pb, ^{161}Tb). Hence, the use of PRRT is anticipated to increase significantly, but this also demands accurate and reliable tools to assess treatment response. Although several established modalities are available to assess NEN, the current response assessment paradigm to PRRT is not well established.

Response to PRRT has often relied on the use of conventional imaging similar to other solid tumour malignancies. However, this alone is inadequate given the significant tumour heterogeneity (within and between patients), variable imaging phenotype and the biological complexity of NEN. Molecular imaging using positron emission tomography computer tomography (PET/CT) has the additional advantages with its unique ability to assess molecular features relevant for NEN, which includes evaluation of tumour SSTR expression and burden (by [^{68}Ga]Ga-DOTA-Octreotate) or tumour metabolic activity ([^{18}F]F-FDG). Importantly, the response to PRRT needs to take into consideration the indications for treatment. Patients treated predominantly for progressive disease necessitate the use of imaging techniques to re-assess tumour size/burden for response. For patients treated for symptoms secondary to hormone hypersecretion, hormone biomarkers or quality of life parameters optimally need to be used. A combination of methods is often required for most patients to provide a comprehensive assessment tailored for the individual patient scenario. Given the complexities, developing a one-size-fits-all response assessment pathway is challenging. Hence, the current expert consensus guidelines support different types and frequency of follow-up according to disease and the clinical setting.[6–11]

We aim to outline the role of anatomical, molecular imaging and biomarkers for response assessment to PRRT for patients with NEN, highlighting the challenges and perspectives for the need to focus on an individualised approach.

2 | ANATOMICAL IMAGING

Accurate response assessment of GEP NEN following treatment with PRRT is challenging and there is no consensus regarding which imaging techniques to use to best assess response.[12,13] Conventional anatomical imaging plays an important role in the initial staging, restaging, treatment response assessment and ongoing monitoring of NEN and is often used in combination with molecular imaging. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most frequently as they are widely available, relatively inexpensive and offer very good contrast and spatial resolution allowing accurate measurements of lesions.[14]

Most GEP NEN are hyper-vascular lesions, frequently with hypervascular hepatic metastatic disease, and therefore it is important that multiphase post contrast imaging is performed both in CT and MRI examinations, including a late arterial phase to best depict the lesions.[15] Both CT and MRI are crucial in the response assessment after PRRT, but each imaging modality has its advantages and disadvantages.

2.1 | CT

CT is widely accessible, inexpensive, fast, with relatively standardised protocols and therefore examinations are easily reproduced. Many patients will have CT imaging at baseline to stage the primary lesion and identify the presence of metastatic disease. However, CT has recognised limited ability to identify small lesions (particularly in the liver), occult primary, small lymph node metastases or bone metastases and uses ionising radiation.[16,17]

2.2 | MRI

MRI offers improved lesion detection, has superior soft tissue resolution in the liver allowing for better detection of small hepatic lesions and intralesional changes.[15,18] MRI does not use ionising radiation and has the added benefit of functional techniques such as diffusion weighted imaging (DWI). DWI is a fast-imaging technique that relies on the difference in Brownian motion of water molecules in the different tissues to obtain contrast. The mobility of water protons is reduced in tumours (which have an increased cellular density), resulting in restricted diffusion which is visible as bright signal on DWI imaging. DWI offers high signal contrast in liver metastases which improves small liver lesion detection.[19,20] Hepatocyte specific MRI contrast agents are absorbed by functioning hepatocytes in the liver, which are absent in neuroendocrine liver metastases. This results in high contrast between the relatively bright signal of the background liver parenchyma and low signal of the metastases. The use of these agents is the technique of choice as it results in increased lesion conspicuity and improved reproducibility of measurements of lesions, and avoids the need for optimal arterial phase contrast imaging which is required with standard contrast agents to best depict hyper-vascular neuroendocrine liver metastases.[20–22] However, MRI is less available and more expensive than CT, the examinations are more lengthy and therefore more prone to imaging artefacts and reduced patient tolerance.

2.3 | Response assessment after PRRT

CT and MRI largely rely on the assessment of lesion size and the detection of new lesions. The tumour response criteria most widely used for this are based on the revised Response Evaluation Criteria in Solid Tumours (RECIST 1.1).[23] The RECIST 1.1 criteria are widely applied in oncology trials to assess tumour response to treatments and are also utilised in the routine evaluation of NEN treatment

response in some expert centres.[24] It is well known that the use of RECIST 1.1 has limitations in assessing tumour response in the generally very slow growing NENs,[13,25–28] and that many treatments, including PRRT, result in delayed growth or disease stabilisation, rather than a reduction in size. RECIST 1.1 only allows limited lesion selection (two lesions per organ, no more than five in total) which is particularly limiting in NEN given the heterogenous nature and does not encompass the evaluation of whole-body disease burden. Moreover, RECIST 1.1 does not include small nodal metastases that are non-enlarged, and bone metastases cannot be included as target lesions unless they have a measurable extra-osseous component. Most importantly RECIST 1.1 does not take into account intralesional treatment response such as necrosis and haemorrhage due to the decreased vascularisation caused by PRRT, which can even lead to a temporary increase in size of a lesion, a phenomenon called 'pseudoprogression.'[12,14,29,30]

Other tumour response criteria in other tumours, such as the Choi criteria and modified RECIST (mRECIST), have so far failed to demonstrate a benefit over standard RECIST in the assessment of tumour response post PRRT. The Choi criteria were proposed in 2007 when dramatic tumour density changes were observed within gastrointestinal tumours following treatment with imatinib, combining changes both in size and density on CT.[24] mRECIST was developed to assess treatment response in hepatocellular carcinoma where the disappearance of all the enhancing tumour portion on arterial phase imaging is considered a complete response.[24,25]

Recently, tumour growth rate (TGR) has been identified as a promising radiological biomarker that could be used to better understand tumour growth dynamics in NEN.[31–33] TGR is based on change in tumour volume per month which can be calculated based on measurements of lesions on CT or MRI.[31,32] It enables identification of subtle changes in tumour growth which can overcome the limitations of RECIST 1.1 in the evaluation of NEN, particularly in those patients with slow-growing tumours.[32] TGR was found to be useful for treatment monitoring, but also as an early radiobiological marker able to predict progression free survival and to identify patients with advanced NEN who may need close radiological follow-up.[31,33] It could also possibly be used in the future to assess response to treatment, including response to PRRT.[33]

There is possibly a role for whole body diffusion weighted MRI in the future to assess for early response to PRRT. Vandecaveye et al. found that the apparent diffusion coefficient (ADC) was a repeatable early response marker and indicator of progression-free and overall survival after PRRT for NEN; however, their study was limited and more research in this area is needed.[34]

3 | MOLECULAR IMAGING

3.1 | Somatostatin receptor (SSTR) PET/CT

It is well established that SSTR represent a useful molecular target for well-differentiated GEP NEN.[35] ^{68}Ga-labelled octreotide derivates DOTATOC, DOTATATE and DOTANOC PET/CT have shown excellent imaging resolution for SSTR expressing NEN.[36–38] [^{G8}Ga]Ga-DOTA-octreotate (^{68}Ga-DOTATATE), ^{68}Ga-DOTATOC, and [^{64}Cu]Cu-DOTA-octreotate are FDA-approved for NEN imaging. Its role in localisation of primary tumour, staging and theranostics selection is well established in consensus guidelines.[39,40] SSTR PET/CT has high sensitivity (range 90%–94%), specificity (90%–92%),[41–43] high management impact (44%), and has incremental value over conventional CT or MRI for identification and localisation of primary small bowel NEN, small lymph node metastases and bone metastases,[16,42,44,45] allowing assessment of the true disease extent of NEN.

Its role in response assessment post PRRT is less defined and prospective data is lacking. Currently, guidelines support SSTR PET/CT restaging after PRRT to serve as a new molecular baseline for future comparisons, recognising the frequent lack of response on anatomical imaging for low grade tumours.[40,46] It is especially useful to monitor NEN lesions that are only visualised on molecular imaging and not anatomical modalities (e.g. small non-enlarged nodes or osseous metastases), at the time of suspected progression with equivocal anatomical findings, and for theranostic assessment.[13,16,40,44] Refer to Figure 1.

However, some recognised limitations of SSTR PET/CT relevant to restaging include the inability to characterise small liver lesions (better defined by arterial phase or hepatocyte specific MRI / CT), and mis-interpretation of variant physiologic or inflammatory activity.[47] Importantly, changes in lesion SSTR intensity by standardised uptake value (SUV) alone does not reflect progression or response. SUV variations may be influenced by several factors: (1) commencement or increase of SSA therapy may lead to relative increase in tumour-to-background ratio and tumours appear more intense[48–50]; (2) significant changes in tumour burden can be associated with tumour sink effect,[14,51] where an anatomical reduction in tumour size (response) could be associated with increase in SSTR intensity likely related to higher concentration of SSTR-expressing differentiated disease; (3) a reduction of lesion intensity associated with an enlarging lesion could reflect de-differentiated disease biology and SSTR imaging must be interpreted with careful review of co-registered CT or anatomical imaging for complex cases; and (4) lack of standardisation of imaging protocols and influence of new scanner technologies on SUV. Refer to Figures 2 and 3 for the roles of multimodality imaging.

To date, only a small number of retrospective studies have investigated the role of SSTR PET in PRRT response assessment. However, evidence is limited as different methodologies were used[52–55] ranging from assessments of functional lesion size, SSTR volume or intensity of uptake, overall showing inconsistent results in outcome prediction, likely related to the small retrospective sample cohorts. Large prospective data using consistent methodology is required.

A standardised response assessment criteria for SSTR PET/CT remain currently undefined but is desperately needed. Further studies should evaluate quantitative uptake parameters and changes in SSTR volumetric data as a potential imaging predictive or prognostic biomarker. To accomplish this, SSTR PET/CT restaging needs to be incorporated into prospective theranostics trials, to generate a

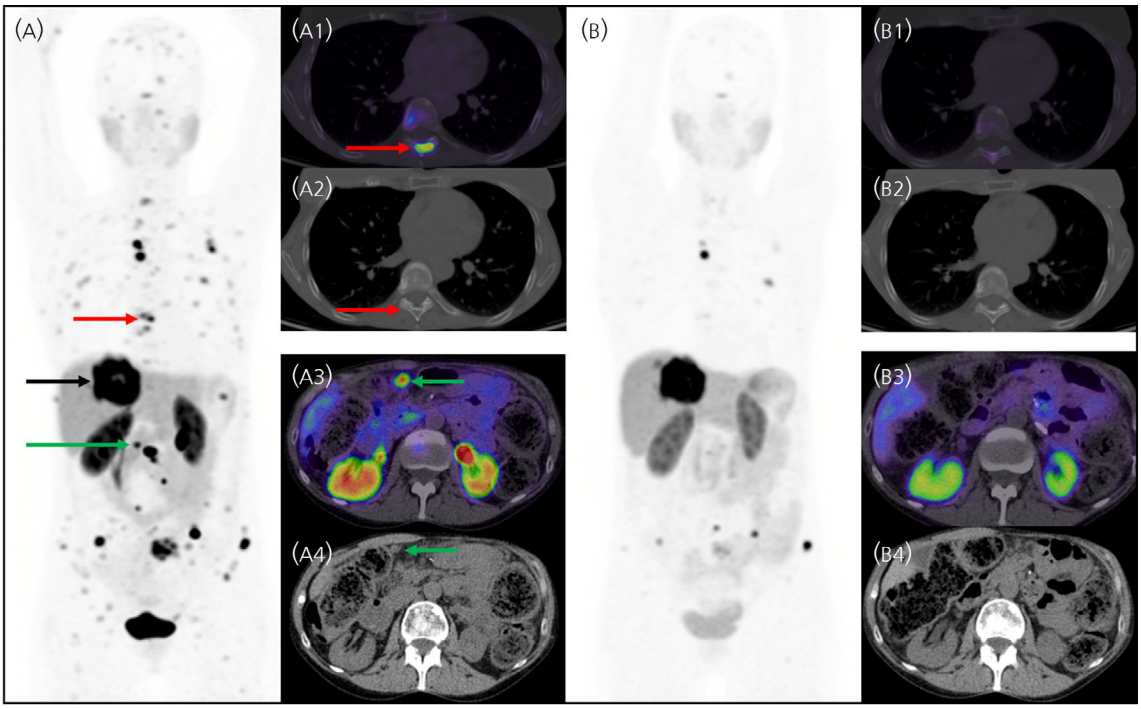

FIGURE 1 Case showing the role of multi-modality imaging for assessment post-PRRT, highlighting the importance of SSTR PET/CT in the diagnosis and response assessment of osseous disease. 63 years old female with metastatic Grade 2 small intestinal NEN. Pre-PRRT ^{68}Ga-DOTATATE PET/CT maximum intensity projection (MIP) images (A): Showed dominant RECIST 1.1 measurable liver metastases (black arrow); but multiple small osseous and nodal involvement were non-measurable on CT, and these were apparent on SSTR imaging. Images A1, A2: Representative small SSTR expressing bone metastases, not visible on CT. Images A3, A4: A small peritoneal metastasis was identified on SSTR imaging, this was non-enlarged and only retrospectively identified on CT. Post PRRT MIP images (B) showed overall reduction of SSTR disease burden. Whilst the dominant liver metastases remain stable based on RECIST 1.1, the other small non-measurable bone and nodal lesions have significantly reduced in avidity and number on PET/CT. Image B1, B2: The bone metastases remain occult on CT. Image B3, B4: The small peritoneal nodule became non-visible. This was accompanied by improvement of symptoms (bone pain), significant improvement of hormone secretory symptoms (flushing and diarrhoea), and reduction of CgA from 821 to 200 μg/L.

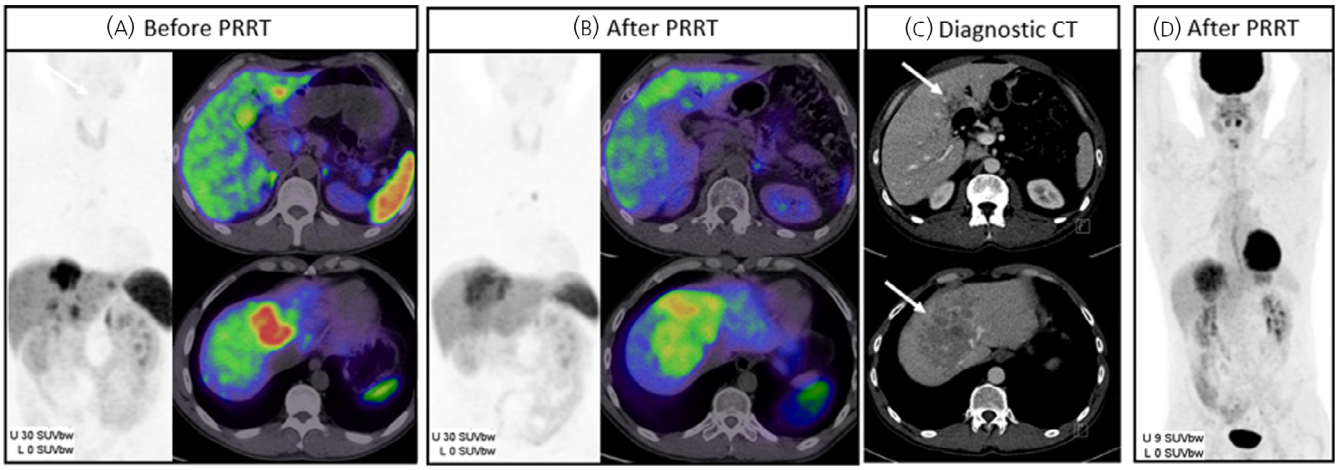

FIGURE 2 Case highlighting the importance of anatomical imaging, and potential limitations of SSTR PET/CT using SUV. 55 years male. PNET G2 10%, with progressive liver metastatic disease. Before PRRT (image A) showed SSTR-expressing liver metastases. After PRRT (B): Interval reduction of SSTR avidity at all sites of disease. However, the most dominant lesion in segment 4 had increased in size, with limited characterisation on low-dose CT (differentials of unusual mixed response, pseudo-progression or de-differentiation). Characterisation with diagnostic CT (C) confirmed a solid enhancing mass in segment 4, without features of necrosis, consistent with disease progression. Note the other smaller PRRT-targeted lesions had reduced in size consistent with mixed treatment response. FDG PET/CT (D) showed associated intense metabolic activity confirming proliferative disease in the solitary progressive segment 4 lesion. Biopsy of this lesion showed G3 disease, Ki-67 70%.

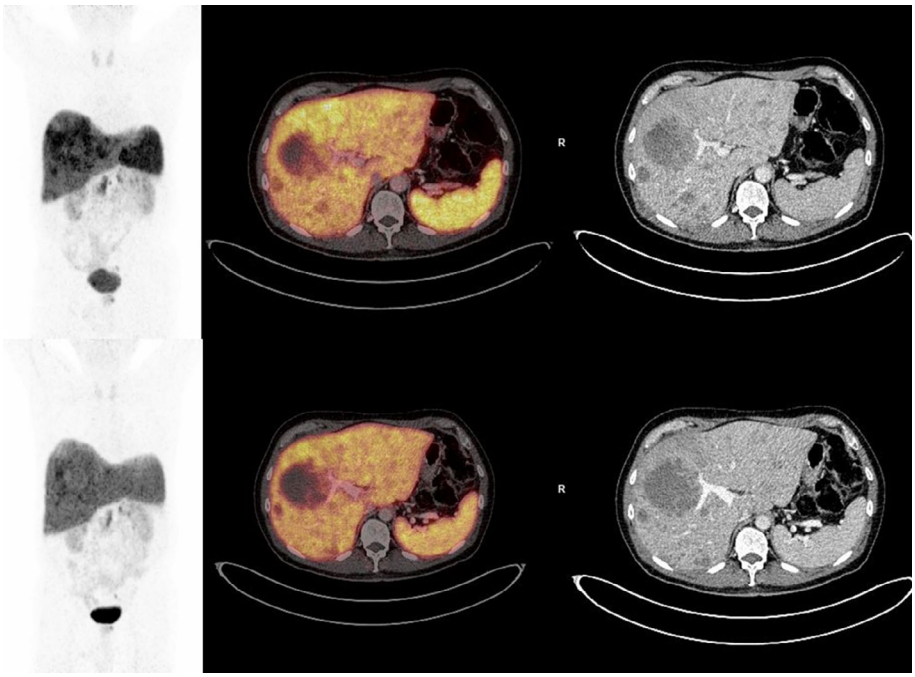

FIGURE 3 57 years old male with a rectum NET and histopathologically confirmed liver metastases (G2, ki67 10%). While many lesions are SSTR-expressing, there were multiple CT-morphologic obvious and SSTR2-negative liver lesions continue to grow over time showing discordant findings (top: Baseline ^{68}Ga-DOTATOC PET/CT from July 2023, bottom: ^{68}Ga-DOTATOC PET/CT performed 4 months later). This highlights that NEN lesions can be heterogenous, in this case not all lesions are SSTR expressing, and anatomical imaging would provide better lesion assessment including for response assessment.

TABLE 1 Pros and cons of anatomical imaging techniques (CT and MRI), and molecular imaging (SSTR and FDG PET/CT) for NEN response assessment imaging.

	Anatomical imaging		Molecular imaging	
	CT	**MRI**	**SSTR PET/CT**	**FDG PET/CT**
Pros	• Accessible • Fast • Standardised protocols • RECIST 1.1	• NEN detection in liver, brain • No ionising radiation • Liver specific contrast agents • Intralesional characterisation • RECIST 1.1	• Highly sensitive for SSTR+ lesions • Small lesions: nodes, occult primary • Non-measurable bone metastases • Quantitative assessment • Whole body assessment	• Marker of metabolic activity • Prognostic • Quantitative assessment
Cons	• Consistent technique is needed: multiphase post-contrast imaging, late arterial phase • Small lesions: liver, nodes, occult primary • Non-measurable lesions (bone)	• Less available • More expensive • More time consuming • Prone to artefacts	• Small liver lesions (background activity) • False-positive findings • Lesion SUV influenced by several factors (eg altered biodistribution)	• False-positive findings

standardised evaluation framework including response evaluation similar to the approach of the PROMISE criteria for prostate cancer assessment using prostate-specific membrane antigen (PSMA) PET/CT.[56]

3.2 | FDG PET/CT

[^{18}F]F-FDG (FDG) is a well-established PET tracer used in clinical oncology for staging and restaging in many cancer types. For NEN, there is evidence that FDG metabolic activity is closely correlated with higher tumour grade (typically Grade 2 or 3 disease), poorly differentiated disease, and worse prognosis.[57–60] There is increasing support to use FDG PET/CT in selected patients with higher grade NEN for theranostics PRRT selection.[13,16] There is an increasing number of studies showing that a dual tracer approach is a useful prognostic imaging biomarker in NEN.[61,62] Its role after PRRT is yet to be established but treatment response to the prognostically significant metabolically active components likely confers important prognostic stratification to this patient cohort with higher-grade disease. Further studies and prospective data are needed to establish its clinical use in this evolving landscape for restaging post PRRT.

Occasionally, treatment-related 'pseudo-progression' can occur, and molecular imaging can be useful to clarify this phenomenon.[10] Refer to Table 1 for a summary of anatomical and molecular imaging.

3.3 | Post-treatment SPECT/CT imaging

Whilst not performed universally, post-PRRT SPECT/CT imaging of γ-emissions are performed in many centres. Images are usually acquired at 4–24 h post administration of [^{177}Lu]Lu-DOTA-Octreotate and can be interpreted by qualitative measures and to perform quantitative dosimetry. This provides information on early changes in response or progression during PRRT cycles and may guide individual management. A change in management in 27% was reported in one series; patients with higher grade tumours had higher rate of management change in terms of progressive disease.[63] Further studies are needed to evaluate its role as an early predictive or prognostic biomarker during PRRT.

4 | BIOMARKERS

4.1 | Chromogranin A (CgA)

Several studies have evaluated longitudinal CgA measurement in monitoring treatment response over time. In a large Dutch retrospective analysis ($N = 354$), overall 265/354 (75%) patients had an elevated CgA at baseline.[30] At 12 weeks after the last therapy, the mean CgA levels in patients with disease control continued to decline, whereas CgA showed a significant increase in patients with progressive disease.[30] Nevertheless, the CGA level can be impacted by demographics, patient comorbidities (cardiac and renal failure, gastritis, hepatitis, inflammatory bowel disease, inflammatory conditions) or medications (steroids, PPIs, H2 antagonists, etc.).[64] At this point, the utility of CgA in this regard is not supported by current guidelines; however, significant trends in CgA levels may be supportive of treatment response.

4.2 | Peptide hormone markers

Up to 30% of NEN are functional, secreting peptide hormones with associated syndromic manifestations which often prompted the diagnostic journey in the first instance. Carcinoid syndrome is found in 20% of patients with NEN.[65] PRRT is effective in the control of tumour load as well as peptide secretion in metastatic functional NEN. The most common secreted peptide hormone is serotonin, followed by catecholamines, insulin and ACTH, all of which have potential for peptide flare or hormonal crisis post PRRT. Therefore, the assessment of peptide hormones in functional NEN not only provides longitudinal evidence for therapeutic response but also assists in risk stratification for patients with uncontrolled peptide secretion with potential peptide flare post PRRT. Less common peptides and their associated syndromes are listed in Table 2.[66–69]

A retrospective study of carcinoid patients who underwent 4 cycles of [^{177}Lu]Lu-DOTA-Octreotate noted a reduction in urine 5-HIAA from average 775 μmol/day to 530 μmol/day after 6 months. All patients with symptomatic improvement post PRRT had a reduction in 5-HIAA.[70] Patients with shorter post-treatment doubling time of urine 5-HIAA had a higher risk of disease progression and disease-specific mortality in a prospective study in which 7% of subjects had PRRT.[71,72] Urine 5-HIAA is recommended to monitor response to PRRT treatment.[63] Food restriction and 24-h collection remains a barrier for patients. More recently, a spot urine 5-HIAA/creatinine ratio of 5.3 mol/mmol was found to be non-inferior (AUC = 0.95, CI 0.90–0.99) and might replace the cumbersome 24-h urine collection for monitoring in the future.[73]

4.3 | Utility of peptide hormone markers post PRRT

Carcinoid crisis has been reported in up to 3.5% of patients with carcinoid syndrome post PRRT.[74] Peptide flare can occur days to 2 weeks post PRRT, therefore an initial increase in hormone concentration does not negate long-term benefits. Follow-up monitoring of peptide hormones is mandatory to down titrate peptide secretion therapy such as glucocorticoids for insulinoma and metyrapone for ectopic ACTH NEN to avoid toxicity. In the absence of a standardised response assessment criteria, a complete peptide response post PRRT can be defined as cessation of peptide blocker (e.g. metyrapone) without symptom relapse and normalisation of peptide profile (e.g. cortisol, ACTH). Conversely, partial peptide response can be defined as dose reduction of peptide blocker without symptom relapse and/or reduced peptide concentration on stable peptide blocker. These definitions are consistent with the monitoring of post-treatment response in functional non-NEN tumours such as primary aldosteronism.[75]

4.4 | Liquid biomarkers

The commercially available NETest and the PRRT Predictive Quotient (PPQ) have demonstrated favourable predictive impact/precision in terms of disease identification and behaviour[76] but also for treatment response (NETest,[77,78] PPQ[77–79]). At present, these biomarkers cannot be recommended for routine clinical care until there is a better understanding on how they definitively play a role in clinical management. This would be best evaluated as part of prospective clinical trials.

The NETest is a transcriptomic signature for NEN based on upregulated NEN tumoural gene co-expression networks measuring circulating 51 marker transcriptomic mRNA signature.[80] The mRNA signature is mathematically interrogated to provide a score, scaled 0%–100%, referred to as the NETest score.[80,81] The NETest metrics for wide clinical applications have been shown to out-perform standard biomarkers such as CgA,[82,83] and as interventional or response biomarker for PRRT.[84]

The baseline PPQ has also undergone development and validation through a series of studies in patients treated with PRRT.[77–79] The

TABLE 2 NA = Not routinely available as a blood based biomarker, however immunohistochemistry staining might be available on tissue specimens.

Secreted peptide hormone (syndrome)	Tests to monitor PRRT response	Symptoms	PRRT response
Serotonin (Carcinoid)	24 h urine 5-hydroxy indole acetic acid (5-HIAA)	Diarrhoea, flushing, labile blood pressure, bronchospasm	^{177}Lu-DOTATATE. *N* = 22. Retrospective. 30% reduction in HIAA in 56%.[70]
Catecholamines (Pheochromocytoma, paraganglioma)	Plasma metanephrines	Hypertension, tachycardia	^{177}Lu-DOTATATE or ^{90}Y-DOTATOC *N* = 201. Systemic review. Biochemical response in 64%[101]
Insulin (Insulinoma)	Insulin, c-peptide, glucose, HbA1c	Hypoglycaemia	^{177}Lu-DOTATATE Or ^{90}Y-DOTATOC. *N* = 26. Retrospective. Transient worsening in 19%, Improved after 17 months in 58%.[102]
ACTH (Ectopic Cushing's)	ACTH, 8 am cortisol, 24 h urine free cortisol	Moonlike facies, striae, hyperglycaemia, hypertension, peripheral oedema	^{177}Lu-DOTATATE. *N* = 13 Retrospective. 77% achieved partial or complete cortisol control.[103]
Gastrin (Zollinger-Ellison)	Gastrin	Peptic ulcer	• ^{177}Lu-DOTATATE Or ^{90}Y-DOTATOC. *N* = 11. Retrospective. Gastrin decreased from 4831 ml/L to 932.6 ml/L, 64% improved or stabilised.[104] • ^{177}Lu-DOTATATE. *N* = 7. Best tumour response PR 71.4%. Mean reduction of gastrin 87% (*N* = 3).[105]
Vasoactive intestinal peptide (VIPoma)	VIP	Secretary diarrhoea, hypokalemia	• ^{177}Lu-DOTATATE. *N* = 1. Case report. VIP normalised at 12 month review.[106] • ^{177}Lu-DOTATATE. *N* = 5. Best tumour response 80%. Mean reduction of VIP 80% (*N* = 2).[105]
Glucagon (Glucagonoma)	Glucagon	Hyperglycaemia	• ^{90}Y-DOTATOC. *N* = 3. 2 responded with 12 m PFS.[107] • ^{177}Lu-DOTATATE. *N* = 8. Best tumour response 50%. Mean reduction of glucagon 87% (*N* = 5).[105]
Calcitonin	Calcitonin	Diarrhoea, flushing	–
Cholecystokinin (CCKoma)	NA	Peptic ulcer, diarrhoea, weight loss	–
Growth hormone releasing hormone (Acromegaly)	GH, IGF-1		–
GLP-1	NA	Hypoglycaemia	–
IGF-2	NA	Hypoglycaemia	–
PTHrP (PTH independent hypercalcemia)	PTHrP, PTH, calcium	Hypercalcemia	–
Renin	Renin, aldosterone	Hypertension	–
Somatostatin (Somatostatinoma)	NA	Cholelithiasis, weight loss, diarrhoea	–
Vasopressin (SIADH)	Copeptin	Hyponatremia	–

PPQ is based upon peripheral blood NET-specific gene cluster expression (growth-factor signalome and metabolome, related to their roles in radiosensitivity) integrated with Ki67 using a logistic regression model.[85,86] The PPQ has been prospectively evaluated using data from 3 independent PRRT studies (*N* = 158).[79] In this pivotal study, treatment response was evaluated using the RECIST 1.1 criteria: in the developmental cohort the PPQ predicted 100% of responders and 84% of non-responders (accuracy: 93%), and in the two validation cohorts the PPQ was 95% accurate.[79] A follow-on analysis from these 3 studies (*N* = 122) evaluated serial NETest and baseline PPQ for patients treated with PRRT: the NETest significantly decreased in RECIST responders ($p < .0001$) and remained increased non-responders ($p < .0005$).[78] The PPQ response prediction demonstrated a 99% accurate positive and 93% accurate negative prediction. Of note CgA did not reflect PRRT treatment response.[78]

4.5 | Other markers

Significant correlates in regard to PFS or OS ($p < .05$) have included serum hepatic biochemistries such as elevated ALT or De Ritis ratio (AST/ALT).[87] Similarly elevated inflammatory markers included neutrophil counts, neutrophil:lymphocyte ratio, PCM (platelet x CRP multiplier)[88,89] and the Inflammatory based index (derived from CRP and albumin).[90,91] However, its role in response assessment is yet to be confirmed.

5 | SYMPTOMS AND QUALITY OF LIFE PARAMETERS

Treatment response should also include the assessment of symptoms and quality of life parameters. In NETTER-1, quality of life assessment was evaluated using the European Organisation for Research and Treatment of Cancer quality-of-life questionnaires QLQ C-30 and G.I. NET-21.[92] Time to QoL deterioration (TTD) was longer in the [^{177}Lu] Lu-DOTA-Octreotate arm versus the control arm for global health status (HR 0.406), physical functioning (HR 0.518), role functioning (HR 0.580), fatigue (HR 0.621), pain (HR 0.566), diarrhoea (HR 0.473), disease-related worries (HR 0.572), and body image (HR 0.425).[92] Improvement in QOL has also been reported in several prior PRRT studies.[93–96] Symptoms and patient-reported outcome or experience measures form an important component of response assessment in patients with NEN and should be incorporated into prospective trials.

6 | SUMMARY OF CURRENT CLINICAL APPROACH AND PERSPECTIVES

The significant heterogeneity and complexity of NEN makes it difficult to formulate a simple monitoring approach for patients post PRRT, highlighting that a composite individualised approach using combined modalities is required.

6.1 | Imaging choice

Anatomical imaging using CT or MRI remains the most available and commonly used method to assess oncologic control or response. This should be performed post-PRRT if lesions are measurable and especially for dominant liver disease. RECIST 1.1 criteria continues to be widely used for theranostics trials. However, SSTR PET/CT is recommended post-PRRT, particularly for patients with small primary lesions, nodal or osseous disease given its high diagnostic accuracy over anatomical imaging in these settings. It can also re-establish lesion SSTR uptake and assess whole body molecular burden. For patients with baseline FDG-avid disease (typically indicating higher grade disease with inferior prognosis), FDG PET/CT may be useful to assess treatment response of these prognostically significant components, and should be considered. Hence, the choice of imaging post-PRRT should be guided by the patient's baseline disease phenotype, disease location and distribution, and a multimodality approach is often required during longer term follow-up after PRRT.

6.2 | Frequency

Response assessment is typically performed 3–6 months after PRRT. Subsequent monitoring frequency should be guided by the disease grade, burden, growth kinetics, and expected mechanism or degree of response.[14,97] In general, patients with low grade indolent or limited disease could be restaged less frequently (such 9–12 months). However, patients with poor prognostic factors such as higher grade, high burden, metastatic FDG-avid disease, aggressive tumour behaviour or severe endocrinopathy[6] would require more frequent imaging with the appropriate conventional and molecular imaging modalities suited to the individual scenario, such as every 3–6 months. Refer to Figure 4 for a suggested imaging approach based on disease grade and baseline phenotype.

6.3 | Biomarkers

Patients treated for hormone-secretory symptoms benefit from clinical review and re-assessment of the relevant hormone markers after PRRT. Although the trend of CgA (a non-specific marker) is useful, clinicians need to be aware of its potential false positive confounding factors. Urine 5-HIAA is a more accurate surrogate of serotonin

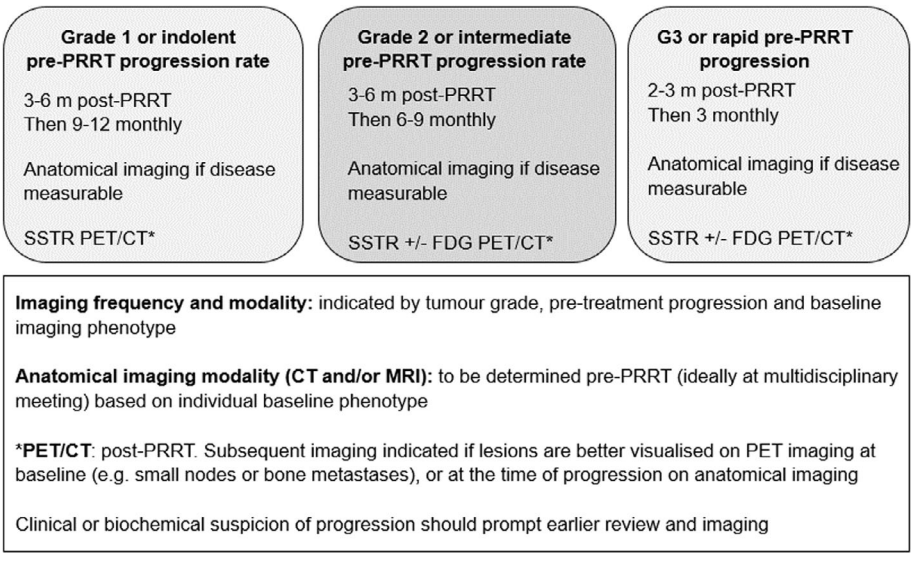

FIGURE 4 Suggested approach for imaging response assessment after PRRT.

secretion and should be measured for response assessment after PRRT and for prognosis in disease specific mortality. Other peptide hormone measurements are individualised according to the relevant secretory syndromes in order to dose-titrate peptide blocking therapies. An immediate increase post PRRT may be due to peptide flare, and markers should be measured at least 4 weeks post PRRT cycle to assess treatment response. Whilst liquid biomarkers NETest and PPQ are potentially beneficial for assessing response after PRRT, they are not universally available at present, nor validated by prospective randomised trials.

7 | FUTURE

Significant imaging advances are expected and being developed. In terms of anatomical imaging, new imaging techniques such as dual energy CT, hybrid imaging, DWI, and dynamic contrast enhanced MRI are potential tools which may further improve individualised response assessment in NEN post PRRT.[12,98,99] Radiomics is a fast-evolving area of research in imaging, this coupled with machine-based learning could in the future provide further insights into tumour response following PRRT[12,24,99] but require further evaluation and validation. In terms of molecular imaging (both SSTR and FDG), the use of quantitative measures such as serial or whole body uptake parameters and changes in volumetric data will likely serve as important biomarkers for restaging, but further evaluation to determine which parameters and its role is warranted. Incorporating restaging PET/CTs is needed for prospective theranostics trials. Machine learning and future developments of automatic contouring programs can accelerate whole body molecular imaging phenotype assessments, advancing into practical use. Standardised definition of SSTR imaging and biomarker response assessment criterion is required for uniform patient assessment, clinical trial planning and comparable research results. In terms of novel biomarkers, more NEN specific biomarkers are needed, requiring a high level of precision and stringent validation, whilst being available for routine clinical care. The potential for longitudinal biomarkers of PRRT response, such as circulating NET cells[100] or circulating tumoural DNA (ctDNA) have yet to be determined.

8 | CONCLUSION

NEN is a complex heterogenous disease. Which modality and how to measure PRRT success need to be tailored for the individual patient in the context of the indication for PRRT (oncological progression or symptoms/uncontrolled hormone secretion, or both). Response to PRRT currently requires a detailed, multimodality and individualised approach, which is best delivered via an expert multidisciplinary team. Anatomical, molecular imaging and peptide biomarker assessment plays a crucial role in this. Future developments of advanced imaging techniques and novel biomarkers will further enhance response assessment to PRRT for individual patients with this complex heterogeneous disease.

AUTHOR CONTRIBUTIONS

Grace Kong: Conceptualization; methodology; supervision; project administration; writing – review and editing; writing – original draft; validation; visualization. **Geertje Noe:** Conceptualization; methodology; validation; writing – original draft; writing – review and editing. **Cherie Chiang:** Conceptualization; methodology; writing – original draft; writing – review and editing; validation. **Ken Herrmann:** Conceptualization; methodology; writing – review and editing; validation. **Thomas A. Hope:** Conceptualization; methodology; validation; writing – review and editing. **Michael Michael:** Conceptualization; methodology; validation; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

There are no direct conflict of interests or funding source reported by co-authors for this article.

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DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Institutional ethics approval is not required for this review article.

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REFERENCES

1. Perren A, Couvelard A, Scoazec JY, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. *Neuroendocrinology*. 2017; 105(3):196-200.
2. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017; 376(2):125-135.
3. Hicks RJ, Kwekkeboom DJ, Krenning E, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. *Neuroendocrinology*. 2017;105: 295-309.
4. Baudin E, Walter T, Beron A, et al. First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177lutetium–octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial. ESMO Congress 2022, Abstract 887O. *Anna Oncol*. 2022;33(Suppl_7):S410-S416.
5. Singh S, Halperin D, Myrehaug S, et al. [(177)Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. 2024;403:2807-2817.

6. Knigge U, Capdevila J, Bartsch DK, et al. ENETS consensus recommendations for the standards of care in neuroendocrine neoplasms: follow-up and documentation. *Neuroendocrinology*. 2017;105(3):310-319.
7. Niederle B, Pape UF, Costa F, et al. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology*. 2016;103(2):125-138.
8. Falconi M, Eriksson B, Kaltsas G, 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):153-171.
9. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology*. 2016;103(2):186-194.
10. Merino-Casabiel X, Aller J, Arbizu J, et al. Consensus document on the progression and treatment response criteria in gastroenteropancreatic neuroendocrine tumors. *Clin Transl Oncol*. 2018;20(12):1522-1528.
11. Singh S, Moody L, Chan DL, et al. Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumors. *JAMA Oncol*. 2018;4(11):1597-1604.
12. Liberini V, Huellner MW, Grimaldi S, et al. The challenge of evaluating response to peptide receptor radionuclide therapy in gastroenteropancreatic neuroendocrine tumors: the present and the future. *Diagnostics (Basel)*. 2020;10(12):1-31.
13. Ambrosini V, Kunikowska J, Baudin E, et al. Consensus on molecular imaging and theranostics in neuroendocrine neoplasms. *Eur J Cancer*. 2021;146:56-73.
14. Galgano SJ, Iravani A, Bodei L, El-Haddad G, Hofman MS, Kong G. Imaging of neuroendocrine neoplasms: monitoring treatment response-AJR expert panel narrative review. *AJR Am J Roentgenol*. 2022;218(5):767-780.
15. Garcia-Carbonero R, Garcia-Figueiras R, Carmona-Bayonas A, et al. Imaging approaches to assess the therapeutic response of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): current perspectives and future trends of an exciting field in development. *Cancer Metastasis Rev*. 2015;34(4):823-842.
16. Sundin A, Arnold R, Baudin E, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. *Neuroendocrinology*. 2017;105(3):212-244.
17. Australia COSo. COSA consensus guidelines for the management of neuroendocrine neoplasms (NENs) [Internet]. 2024. http:// www.cosa.org.au.
18. Lo GC, Kambadakone A. MR imaging of pancreatic neuroendocrine tumors. *Magn Reson Imaging Clin N Am*. 2018;26(3):391-403.
19. d'Assignies G, Fina P, Bruno O, et al. High sensitivity of diffusion-weighted MR imaging for the detection of liver metastases from neuroendocrine tumors: comparison with T2-weighted and dynamic gadolinium-enhanced MR imaging. *Radiology*. 2013;268(2):390-399.
20. Lavelle LP, O'Neill AC, McMahon CJ, et al. Is diffusion-weighted MRI sufficient for follow-up of neuroendocrine tumour liver metastases? *Clin Radiol*. 2016;71(9):863-868.
21. Roll W, Weckesser M, Seifert R, Bodei L, Rahbar K. Imaging and liquid biopsy in the prediction and evaluation of response to PRRT in neuroendocrine tumors: implications for patient management. *Eur J Nucl Med Mol Imaging*. 2021;48(12):4016-4027.
22. Morse B, Jeong D, Thomas K, Diallo D, Strosberg JR. Magnetic resonance imaging of neuroendocrine tumor hepatic metastases: does hepatobiliary phase imaging improve lesion conspicuity and interobserver agreement of lesion measurements? *Pancreas*. 2017;46(9):1219-1224.
23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
24. Ronot M, Dioguardi Burgio M, Gregory J, et al. Appropriate use of morphological imaging for assessing treatment response and disease progression of neuroendocrine tumors. *Best Pract Res Clin Endocrinol Metab*. 2023;37(5):101827.
25. van Treijen MJC, Schoevers JMH, Heeres BC, et al. Defining disease status in gastroenteropancreatic neuroendocrine tumors: Choi-criteria or RECIST? *Abdom Radiol (NY)*. 2022;47(3):1071-1081.
26. Dromain C, Pavel M, Ronot M, et al. Response heterogeneity as a new biomarker of treatment response in patients with neuroendocrine tumors. *Future Oncol*. 2023;19(32):2171-2183.
27. Vullierme MP, Ruszniewski P, de Mestier L. Are recist criteria adequate in assessing the response to therapy in metastatic NEN? *Rev Endocr Metab Disord*. 2021;22(3):637-645.
28. Oberg K, Krenning E, Sundin A, et al. A Delphic consensus assessment: imaging and biomarkers in gastroenteropancreatic neuroendocrine tumor disease management. *Endocr Connect*. 2016;5(5):174-187.
29. Zwirtz K, Hardt J, Acker G, et al. Comparison of Choi, RECIST and somatostatin receptor PET/CT based criteria for the evaluation of response and response prediction to PRRT. *Pharmaceutics*. 2022;14(6):1278-1293.
30. Brabander T, van der Zwan WA, Teunissen JJM, et al. Pitfalls in the response evaluation after peptide receptor radionuclide therapy with [(177)Lu-DOTA(0),Tyr(3)]octreotate. *Endocr Relat Cancer*. 2017;24(5):243-251.
31. Dromain C, Pavel ME, Ruszniewski P, et al. Tumor growth rate as a metric of progression, response, and prognosis in pancreatic and intestinal neuroendocrine tumors. *BMC Cancer*. 2019;19(1):66.
32. Dromain C, Sundin A, Najran P, et al. Tumor growth rate to predict the outcome of patients with neuroendocrine tumors: performance and sources of variability. *Neuroendocrinology*. 2021;111(9):831-839.
33. Lamarca A, Crona J, Ronot M, et al. Value of tumor growth rate (TGR) as an early biomarker predictor of Patients' outcome in neuroendocrine tumors (NET)-the GREPONET study. *Oncologist*. 2019;24(11):e1082-e1090.
34. Vandecaveye V, Dresen RC, Pauwels E, et al. Early whole-body diffusion-weighted MRI helps predict long-term outcome following peptide receptor radionuclide therapy for metastatic neuroendocrine tumors. *Radiol Imaging Cancer*. 2022;4(3):e210095.
35. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. *Eur J Nucl Med Mol Imaging*. 2003;30(5):781-793.
36. Ambrosini V, Morigi JJ, Nanni C, Castellucci P, Fanti S. Current status of PET imaging of neuroendocrine tumours ([18F]FDOPA, [68Ga]tracers, [11C]/[18F]-HTP). *Quart J Nucl Med Mol Imaging*. 2015;59(1):58-69.
37. Treglia G, Castaldi P, Rindi G, Giordano A, Rufini V. Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. *Endocrine*. 2012;42(1):80-87.
38. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med*. 2007;48(4):508-518.
39. Hope TA, Bodei L, Chan JA, et al. NANETS/SNMMI consensus statement on patient selection and appropriate use of (177)Lu-DOTATATE peptide receptor radionuclide therapy. *J Nucl Med*. 2020;61(2):222-227.
40. Hope TA, Allen-Auerbach M, Bodei L, et al. SNMMI procedure standard/EANM practice guideline for SSTR PET: imaging neuroendocrine tumors. *J Nucl Med*. 2023;64(2):204-210.
41. Deppen SA, Blume J, Bobbey AJ, et al. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl Med*. 2016;57(6):872-878.

42. M. Sadowski S, Neychev V, Millo C, et al. Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-Entero-pancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol*. 2016;34(6):588-596.
43. Skoura E, Michopoulou S, Mohmaduvesh M, et al. The impact of 68Ga-DOTATATE PET/CT imaging on Management of Patients with neuroendocrine tumors: experience from a National Referral Center in the United Kingdom. *J Nucl Med*. 2016;57(1):34-40.
44. Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. *J Nucl Med*. 2018;59(1):66-74.
45. Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with (68)Ga-DOTA-conjugated somatostatin receptor targeting peptides and (18)F-DOPA. *Eur J Nucl Med Mol Imaging*. 2017;44(9):1588-1601.
46. Hope TA. Updates to the appropriate-use criteria for somatostatin receptor PET. *J Nucl Med*. 2020;61(12):1764.
47. S. Hofman M, Eddie Lau WF, J. Hicks R. Somatostatin receptor imaging with68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. *Radiographics*. 2015;35(2):500-516.
48. H. Cherk M, Kong G, J. Hicks R, S. Hofman M. Changes in biodistribution on 68Ga-DOTA-Octreotate PET/CT after long acting somatostatin analogue therapy in neuroendocrine tumour patients may result in pseudoprogression. *Cancer Imaging*. 2018;18(1):1-9.
49. Ayati N, Ting Lee S, Zakavi R, et al. Long-acting somatostatin analog therapy differentially alters 68Ga-DOTATATE uptake in Normal tissues compared with primary tumors and metastatic lesions. *J Nucl Med*. 2018;59(2):223-227.
50. Galne A, Almquist H, Almquist M, et al. A prospective observational study to evaluate the effects of long-acting somatostatin analogs on (68)Ga-DOTATATE uptake in patients with neuroendocrine tumors. *J Nucl Med*. 2019;60(12):1717-1723.
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):50-56.
52. Gabriel M, Oberauer A, Dobrozemsky G, et al. 68Ga-DOTA-Tyr3--octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. *J Nucl Med*. 2009;50(9):1427-1434.
53. Haug AR, Auernhammer CJ, Wangler B, et al. 68Ga-DOTATATE PET/CT for the early prediction of response to somatostatin receptor-mediated radionuclide therapy in patients with well-differentiated neuroendocrine tumors. *J Nucl Med*. 2010;51(9):1349-1356.
54. Kong G, Thompson M, Collins M, 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):1831-1844.
55. Huizing DMV, Aalbersberg EA, Versleijen MWJ, et al. Early response assessment and prediction of overall survival after peptide receptor radionuclide therapy. *Cancer Imaging*. 2020;20(1):57.
56. Seifert R, Emmett L, Rowe SP, et al. Second version of the prostate cancer molecular imaging standardized evaluation framework including response evaluation for clinical trials (PROMISE V2). *Eur Urol*. 2023;83(5):405-412.
57. Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res*. 2010;16(3):978-985.
58. Garin E, Le Jeune F, Devillers A, et al. Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. *J Nucl Med*. 2009;50(6):858-864.
59. Heetfeld M, Chougnet CN, Olsen IH, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2015;22(4):657-664.
60. Zhang P, Yu J, Li J, et al. Clinical and prognostic value of PET/CT imaging with combination of (68)Ga-DOTATATE and (18)F-FDG in gastroenteropancreatic neuroendocrine neoplasms. *Contrast Media Mol Imaging*. 2018;2018:2340389.
61. Chan DL, Pavlakis N, Schembri GP, et al. Dual somatostatin receptor/FDG PET/CT imaging in metastatic neuroendocrine tumours: proposal for a novel grading scheme with prognostic significance. *Theranostics*. 2017;7(5):1149-1158.
62. Carideo L, Prosperi D, Panzuto F, et al. Role of combined [(68)Ga]Ga-DOTA-SST analogues and [(18)F]FDG PET/CT in the management of GEP-NENs: a systematic review. *J Clin Med*. 2019;8(7):1032-1044.
63. Yadav S, Lawhn-Heath C, Paciorek A, et al. The impact of posttreatment imaging in peptide receptor radionuclide therapy. *J Nucl Med*. 2024;65(3):409-415.
64. Gkolfinopoulos S, Tsapakidis K, Papadimitriou K, Papamichael D, Kountourakis P. Chromogranin a as a valid marker in oncology: clinical application or false hopes? *World J Methodol*. 2017;7(1):9-15.
65. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18(4):525-534.
66. Oberg K, Couvelard A, Delle Fave G, et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: biochemical markers. *Neuroendocrinology*. 2017;105(3):201-211.
67. Langer P, Bartsch D, Gerdes B, et al. Renin producing neuroendocrine pancreatic carcinoma – a case report and review of the literature. *Exp Clin Endocrinol Diabet*. 2002;110(1):43-49.
68. Roberts RE, Zhao M, Whitelaw BC, et al. GLP-1 and glucagon secretion from a pancreatic neuroendocrine tumor causing diabetes and hyperinsulinemic hypoglycemia. *J Clin Endocrinol Metab*. 2012;97(9):3039-3045.
69. Bergsma H, Konijnenberg MW, Kam BL, 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):453-463.
70. Zandee WT, Brabander T, Blažević A, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE for symptomatic control of refractory carcinoid syndrome. *J Clin Endocrinol Metab*. 2021;106(9):e3665-e3672.
71. Grozinsky-Glasberg S, Davar J, Hofland J, et al. European neuroendocrine tumor society (ENETS) 2022 guidance paper for carcinoid syndrome and carcinoid heart disease. *J Neuroendocrinol*. 2022;34(7):e13146.
72. Tirosh A, Nilubol N, Patel D, Kebebew E. Prognostic utility of 24-hour urinary 5-HIAA doubling time in patients with neuroendocrine tumors. *Endocr Pract*. 2018;24(8):710-717.
73. Calanchini M, Tadman M, Krogh J, Fabbri A, Grossman A, Shine B. Measurement of urinary 5-HIAA: correlation between spot versus 24-h urine collection. *Endocr Connect*. 2019;8(8):1082-1088.
74. Tapia Rico G, Li M, Pavlakis N, Cehic G, Price TJ. Prevention and management of carcinoid crises in patients with high-risk neuroendocrine tumours undergoing peptide receptor radionuclide therapy (PRRT): literature review and case series from two Australian tertiary medical institutions. *Cancer Treat Rev*. 2018;66:1-6.
75. Miller BS, Turcu AF, Nanba AT, et al. Refining the definitions of biochemical and clinical cure for primary aldosteronism using the primary aldosteronism surgical outcome (PASO) classification system. *World J Surg*. 2018;42(2):453-463.
76. Malczewska A, Bodei L, Kidd M, Modlin IM. Blood mRNA measurement (NETest) for neuroendocrine tumor diagnosis of image-negative liver metastatic disease. *J Clin Endocrinol Metab*. 2019;104(3):867-872.

77. Bodei L, Kidd M, Modlin IM, et al. Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2016;43(5):839-851.
78. Bodei L, Kidd MS, Singh A, et al. PRRT neuroendocrine tumor response monitored using circulating transcript analysis: the NETest. *Eur J Nucl Med Mol Imaging*. 2020;47(4):895-906.
79. Bodei L, Kidd MS, Singh A, et al. PRRT genomic signature in blood for prediction of (177)Lu-octreotate efficacy. *Eur J Nucl Med Mol Imaging*. 2018;45(7):1155-1169.
80. Modlin IM, Kidd M, Malczewska A, et al. The NETest: the clinical utility of multigene blood analysis in the diagnosis and management of neuroendocrine tumors. *Endocrinol Metab Clin North Am*. 2018;47(3):485-504.
81. Malczewska A, Kos-Kudla B, Kidd M, et al. The clinical applications of a multigene liquid biopsy (NETest) in neuroendocrine tumors. *Adv Med Sci*. 2020;65(1):18-29.
82. Pavel M, Jann H, Prasad V, Drozdov I, Modlin IM, Kidd M. NET blood transcript analysis defines the crossing of the clinical Rubicon: when stable disease becomes progressive. *Neuroendocrinology*. 2017;104(2):170-182.
83. van Treijen MJC, van der Zee D, Heeres BC, et al. Blood molecular genomic analysis predicts the disease course of gastroenteropancreatic neuroendocrine tumor patients: a validation study of the predictive value of the NETest(R). *Neuroendocrinology*. 2021;111(6):586-598.
84. Oberg K, Califano A, Strosberg JR, et al. A meta-analysis of the accuracy of a neuroendocrine tumor mRNA genomic biomarker (NETest) in blood. *Ann Oncol*. 2020;31(2):202-212.
85. Hill RP. The changing paradigm of tumour response to irradiation. *Br J Radiol*. 2017;90(1069):20160474.
86. Kidd M, Modlin IM. Therapy: the role of liquid biopsies to manage and predict PRRT for NETs. *Nat Rev Gastroenterol Hepatol*. 2017;14(6):331-332.
87. Ruhwedel T, Rogasch JMM, Huang K, et al. The prognostic value of the De Ritis ratio for progression-free survival in patients with NET undergoing [(177)Lu]Lu-DOTATOC-PRRT: a retrospective analysis. *Cancers (Basel)*. 2021;13(4):635-647.
88. Ohlendorf F, Werner RA, Henkenberens C, et al. Predictive and prognostic impact of blood-based inflammatory biomarkers in patients with gastroenteropancreatic neuroendocrine tumors commencing peptide receptor radionuclide therapy. *Diagnostics (Basel)*. 2021;11(3):504-516.
89. de Lima BAM, da Silva RG, Carroll C, et al. Neutrophil to lymphocyte ratio as a prognosis biomarker of PRRT in NET patients. *Endocrine*. 2022;78(1):177-185.
90. Pauwels E, Van Binnebeek S, Vandecaveye V, et al. Inflammation-based index and (68)Ga-DOTATOC PET-derived uptake and volumetric parameters predict outcome in neuroendocrine tumor patients treated with (90)Y-DOTATOC. *J Nucl Med*. 2020;61(7):1014-1020.
91. Black JRM, Atkinson SR, Singh A, Evans J, Sharma R. The inflammation-based index can predict response and improve patient selection in NETs treated with PRRT: a pilot study. *J Clin Endocrinol Metab*. 2019;104(2):285-292.
92. Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with (177)Lu-Dotatate in the phase III NETTER-1 trial. *J Clin Oncol*. 2018;36(25):2578-2584.
93. 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):2724-2729.
94. Martini C, Buxbaum S, Rodrigues M, 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):1566-1573.
95. Marinova M, Mucke M, Mahlberg 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.
96. 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):1361-1368.
97. Kong GHR. Radionuclide imaging of NENs. *Curr Opin Endocr Metab Res*. 2021;18:207-215.
98. Weikert T, Maas OC, Haas T, et al. Early prediction of treatment response of neuroendocrine hepatic metastases after peptide receptor radionuclide therapy with (90)Y-DOTATOC using diffusion weighted and dynamic contrast-enhanced MRI. *Contrast Media Mol Imaging*. 2019;2019:1517208.
99. Saleh M, Bhosale PR, Yano M, et al. New frontiers in imaging including radiomics updates for pancreatic neuroendocrine neoplasms. *Abdom Radiol (NY)*. 2022;47(9):3078-3100.
100. Sun N, Yang Y, Miao H, et al. Discovery and characterization of circulating tumor cell clusters in neuroendocrine tumor patients using nanosubstrate-embedded microchips. *Biosens Bioelectron*. 2022;199:113854.
101. Satapathy S, Mittal BR, Bhansali A. Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2019;91(6):718-727.
102. Friebe L, Freitag MT, Braun M, et al. Peptide receptor radionuclide therapy is effective for clinical control of symptomatic metastatic insulinoma: a long-term retrospective analysis. *J Nucl Med*. 2024;65(2):228-235.
103. Davi MV, Cosaro E, Piacentini S, et al. Prognostic factors in ectopic Cushing's syndrome due to neuroendocrine tumors: a multicenter study. *Eur J Endocrinol*. 2017;176(4):453-461.
104. Grozinsky-Glasberg S, Barak D, Fraenkel M, et al. Peptide receptor radioligand therapy is an effective treatment for the long-term stabilization of malignant gastrinomas. *Cancer*. 2011;117(7):1377-1385.
105. Zandee WT, Brabander T, Blazevic A, et al. Symptomatic and radiological response to 177Lu-DOTATATE for the treatment of functioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab*. 2019;104(4):1336-1344.
106. Audil HY, Eiring RA, Kendi AT, Halfdanarson TR. A case of metastatic VIPoma with complete response to peptide radionuclide receptor therapy. *Pancreas*. 2021;50(4):e45-e46.
107. 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 (Oxf)*. 2011;74(5):593-598.

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