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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

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Abstract

Assessing the response to systemic therapy in neuroendocrine tumors (NET) is challenging since morphological imaging response is often delayed and not necessarily reflective of clinical benefit. Peptide receptor radionuclide therapy (PRRT) has a complex mechanism of action, further complicating response assessment. In response to these challenges, the European Neuroendocrine Tumor Society (ENETS) Theranostics Task Force conducted a statement-based survey among experts to identify the current landscape and unmet needs in PRRT response assessment. The survey, presented at the 2022 ENETS Advisory Board (AB) meeting in Vienna, was completed by 70% of AB members, most of whom (81%) were from ENETS Centers of Excellence (CoE). It comprised a set of 13 questions with two substatements in three questions. Six (46%) of the statements achieved more than 75% agreement, while five (39%) additional statements reached over 60% consensus. Key points from the survey include: AB members agreed that lesions deemed equivocal on computed tomography (CT) or magnetic resonance imaging (MRI) should be characterized by somatostatin receptor (SST) positron emission tomography (PET)/CT before being designated as target lesions. It was agreed that interim response assessments should occur after the second or third PRRT cycle. Over half (54%) preferred using both conventional cross-sectional imaging (CT and/or MRI) and hybrid imaging (SST PET/CT)

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for this purpose. Almost all AB members supported further response assessment 3 months after the final PRRT cycle. A majority (62%) preferred using a combination of conventional cross-sectional imaging and SST PET/CT. For cases showing equivocal progression (ambiguous lesions or nontarget lesions) on CT and/or MRI, further confirmation using SST PET/CT was recommended. A significant majority (74%) preferred assessing pseudoprogression and delayed response by combining SST PET with diagnostic CT and/ or MRI. Though just below the 75% consensus threshold, there was substantial agreement on selecting target lesions based on SST PET/CT uptake intensity and homogeneity. Sixty-nine percent noted the importance of documenting and closely following heterogeneity in lesions in liver, lymph nodes, primary tumors, or other organs. As to the statement on parameters for new response criteria, AB members recommended exploring maximum standard unit value, tumor-to-background ratio, Hounsfield Unit (Choi Criteria), total tumor burden, and novel serum or molecular markers for future response evaluation criteria. Sixty-five percent supported the use of a single SST PET/CT for response assessment of NET lesions treated with PRRT. These findings highlight the importance of integrating advanced imaging techniques and recognizing the need for more nuanced criteria in assessing the efficacy of PRRT in NET patients. This approach aims to enhance the accuracy of treatment monitoring and improve patient outcomes.

KEYWORDS
neuroendocrine tumors, PRRT, RECIST 1.1, response assessment, somatostatin receptor PET/CT

1 | INTRODUCTION

Assessment of response to systemic therapy in neuroendocrine tumors (NETs) is an evolving field because of the challenges posed by slower growth than observed with most other cancers and heterogeneous behavior of the disease both spontaneously and, particularly, in response to treatment. Since patients may have symptoms related to hormone secretion or directly due to mechanical effects of tumor deposits, the motivation for treatment may be more oriented to improving quality-of-life (QOL) than prolonging survival, which may already be relatively long due to the indolent nature of well-differentiated NET. Indeed, QOL benefits have been demonstrated even in the absence of morphological response to therapy [1]. In such cases, laboratory testing and patient-reported outcomes become important objective measures of response [2].

For more aggressive NET, oncological control becomes a higher priority and robust assessment of treatment response becomes important both as a guide to prognosis and to inform ongoing treatment options. While RECIST 1.1 can be an important and powerful tool in clinical trials, with standard outcome endpoints generally acting as surrogates for survival measures [2], its role in guiding treatment of individual patients remains uncertain. For logistic ease in clinical trials, the original RECIST methodology was simplified as much as possible. Size measurement was decided to be taken to include measurement only in one dimension, the longest diameter of each lesion and restricted the number of lesions to be assessed by measurement to a maximum of five lesions (up to two per organ). This is considered to be accurate enough (expected error acceptably small) for large cohorts in controlled trials on cancers with a relatively homogenous and somewhat predictable behavior but lacks full assessment of tumor burden volumetrically. The RECIST response categories and the cut-offs are also used in individual assessments, at least to compare the patient's status with study data. Routine clinical interpretation of disease status on computed tomography (CT) and/or magnetic resonance imaging (MRI) and formal RECIST 1.1 interpretation are found to be discrepant in up to 35% of patients [3]. The majority of these discrepancies are due to fine differences in disease progression and stable disease. Erroneous target lesion measurements (58%), incorrect diagnosis of nontarget progression (30%), and misclassification of new lesions as cancer (11%) are the most common causes of this discrepancy [3]. Measurement variability and inter- and intralesional heterogeneity of tumors are the two major limitations for tumor response evaluation [4].

Exclusive size analysis ignores the complexity of tumor deposits, particularly when there is a significant stromal element that may persist despite a reduction in the malignant cell population or alteration in its biology. Stromal contribution to tumors is a subject of recent interest both diagnostically and therapeutically through the development of imaging approaches to cancer-associated fibroblasts. These particularly include the use of fibroblast activation protein inhibitors (FAPIs) positron emission tomography (PET) [5]. Further, necrosis with or without scarring can lead to residual, non-viable elements that

remain measurable by anatomical techniques but are often better to be characterized on molecular imaging, with [^{18}F]-fluorodeoxyglucose (FDG) PET and somatostatin receptor (SST) PET, when performed in a sufficient time interval after the treatment delivery. Clonal heterogeneity in malignant tumors may evolve over time, either spontaneously or in response to treatment, reflecting the differential response of cancer cells to various therapies. This heterogeneity can be demonstrated by comparing molecular imaging (SST PET ± FDG PET/CT) and morphological imaging (CT, MRI) [6–8]. Assessment of SST heterogeneity becomes even more relevant for high-grade NETs that have a higher likelihood of harboring non-SST-expressing malignant cells. [9]. As a result, when characterizing tumor heterogeneity and response to treatment using morphological and molecular imaging, it is imperative to consider all potential clinical scenarios, including dedifferentiation, necrosis, and second malignancy, and discuss these in the context of a multidisciplinary tumor board.

Peptide receptor radionuclide therapy (PRRT) has taken a central role in the management of gastroenteropancreatic NETs [10]. The mechanism of action of PRRT is complex with both disease regression and progression tending to be much slower than with other forms of cancer treatment. Persistence of residual lesions on anatomical imaging and demonstration of ongoing target expression on molecular imaging allows PRRT to be delivered as multiple treatment cycles spread over many months. While this allows the potential delivery of high cumulative radiation doses to sites of disease, it also makes assessment of interim response for prognostic purposes difficult and limits the ability to modify treatment in response to either refractory or highly responsive disease. As with most cancers, rapid and marked regression of lesions on CT or MRI is a powerful indicator of response. The problem with PRRT is that the change in size of the well to intermediate grade NETs tends to be slow and less marked. Thus, the primary benefit of anatomical imaging is identifying extreme early responders or aggressive primary refractory disease. In a post hoc analysis of the relationship between objective tumor shrinkage and progression-free survival (PFS) in the NETTER-1 population, tumor shrinkage between baseline and 150 days posttreatment was associated with improved PFS for the octreotide arm (hazard ratio [HR]: 0.914; 95% confidence interval [CI]: 0.860–0.971; $p = .0034$) [11]. For the ^{177}Lu-DOTATATE group, the PFS was not significantly affected by tumor shrinkage (HR: 1.006; 95% CI: 0.982–1.03; $p = .623$). These analyses demonstrated that ^{177}Lu-DOTATATE prolonged PFS even when there was no tumor objective response. Delayed response and pseudo-progression may explain this observation [12]. It has been shown that pseudo-progression can be noted in up to 10% of patients [13–16]. One plausible explanation for pseudo-progression is radiation-induced edema and necrosis causing the apparent increase in size, which can be more pronounced with alpha radionuclides. Delayed response has also been reported with tumor regression up to 3 years after ^{177}Lu-DOTATATE [14,17].

Recognizing some of these limitations, the potential benefits of integrating functional information into the response assessment of PRRT, a Theranostics Task Force of the ENETS surveyed opinions of NET experts within its Advisory Board (AB) to (a) understand if there is a need to explore new imaging parameters and response evaluation criteria for PRRT and (b) to provide guidance for potentially useful parameters for testing in prospective or registry-based clinical trials. Sixty-six experts attending the November 2022 ENETS (European Neuroendocrine Tumor Society) AB meeting were asked to rate a set of statements as "in agreement," "in disagreement," "neither in agreement nor in disagreement," or "I am not an expert." They were requested to do so based on their current understanding of the issues with respect to the PRRT response assessment.

2 | METHODS

A set of statements related to response assessment of PRRT in NET in different settings were initially proposed by two authors, VP and VA, and circulated within the ENETS Theranostics Task Force (Gastroenterology $n = 3$, Oncology n = 3, Endocrinology $n = 5$, Surgery $n = 2$, Radiology n = 2, Nuclear Medicine = 4, and Pathology/Molecular Biology n = 2) for discussion, revision, and final approval. One participant was double board certified in both nuclear medicine and radiology but primarily worked as a radiologist for the last 10 years. The revised set of statements (13 in total, and three subquestions; shown in Table 1) was submitted to the attendees (attending either onsite or remotely) of the November 2022 ENETS AB meeting. Respondents were asked to rate each statement using four categories: agree, disagree, neutral, or abstaining as not an expert. Completed forms were collected by the ENETS office. Answers of the respondents declaring themselves as "not an expert" in that particular setting were excluded from the analysis. Agreement among respondents was defined as concordance of at least 75% of answers, whereas statements achieving more than 60% concordance were considered to have achieved support consensus. Results were rounded up to the nearest percent.

3 | RESULTS

The AB meeting attendees included 66 NET specialists. The survey was distributed to 64 attendees, excluding VA and VP, who were involved in drafting the initial set of statements. Forty-seven of the AB attendees returned the forms, which were either sent remotely after the meeting or collected onsite by the ENETS office representatives. On one of the surveys, no name was provided; therefore, to maintain consistency, it was excluded from the analysis, resulting in an overall response rate of 72%. The majority of respondents were from Europe, representing ENETS centers of excellence (41 out of 46), and some respondents (5 out of 46) were from other regions (Argentina, India, Australia, USA). The responses gathered from this survey reflect the perspectives of multidisciplinary experts across all specialties actively involved in NET management, as shown in Table 2.

Respondents' survey results are shown in Table 3. Six (46%) statements attained agreement among more than 75% of the respondents,

TABLE 1 Statement-based survey of the European Neuroendocrine Tumor Society (ENETS) Theranostics Task Force presented at the 2022 ENETS Advisory Board meeting in Vienna, aiming at identifying the current landscape and unmet needs in PRRT response assessment.

No.	Statement
1	SST PET/CT should be used in the response assessment of NET to PRRT
2	In PRRT-treated patients, SST PET in combination with morphologic imaging by diagnostic CT or MRI is useful to assess pseudo-progression and delayed response
3	Equivocal[a] lesions on CT and/or MRI need further characterization using SST PET/CT
4	Selection of target liver lesions on SST PET/CT should be based not only on intensity of somatostatin receptor expression but also on its heterogeneity
5	Total tumor body burden (visual/quantitative on SST PET/CT) and its change during follow-up should be taken into account for response to PRRT
6	Target lesions in liver, lymph nodes, primary tumor as well as other visceral metastases with heterogeneous SST expression on PET/CT should be documented and followed up separately
7	Interim response assessment should be performed after 2nd or 3rd cycle of PRRT
7a	Answer only IF you agree to previous statement. Your preferred option would be (both options can be selected with an X sign) 1. SST PET/CT (diagnostic CT) 2. CT and/or MRI
8	Final therapy response assessment (3 months after last therapy cycles) should be performed
8a	Answer only IF you agree to previous statement. Your preferred option would be (both options can be selected with an X sign) 1. SST PET/CT (diagnostic CT) 2. CT and/or MRI
9	Patients treated with PRRT and showing equivocal progression[b] on CT/MRI in subsequent follow-ups should be further examined for confirmation of PD
9a	Answer only IF you agree to previous statement. Your preferred option would be (both options can be selected with an X sign) 1. SST PET/CT (diagnostic CT) 2. CT and/or MRI
10	Imaging parameters beyond size measurement, like SUVmax, tumor-to-background ratio (TBR), and HU (analog to Choi criteria for gastrointestinal stoma tumors), need to be further evaluated, for example, prospectively or in larger multicenter register studies
11	Integration of novel biomarkers into imaging-based response evaluation should be further evaluated, for example, prospectively or in register-based studies
12	SST PET/CT-based response evaluation should include unconfirmed PD as a subset of response
13	Current evidence on tumor growth rate (TGR), measured on CT or MRI suggests its great potential in prediction of response to PRRT

Abbreviations: CT, computed tomography; FDG, [18F]-fluorodeoxyglucose; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SST, somatostatin receptor.

[a]Equivocal lesion: equivocal lesions can be defined as lesions for which the radiologist is unsure whether they effectively correspond to the designated malignant disease.

[b]Equivocal progression: based on ambiguous lesion or nontarget lesion.

whereas five (39%) attained support from more than 60% of the attendees.

AB members agreed (Q3, Table 1) that equivocal lesions on CT or MRI (i.e., lesions for which the radiologist is unsure whether they should be designated as malignant disease) should be further characterized by SST PET/CT. The issue of interim response assessment was critically discussed, and consensus was reached that it should be performed after the second or third PRRT cycle (Q7, Table 1). As to the method for interim assessment, conclusion was unclear (Table 3, statement 7a).

Almost unanimously (89%), AB members agreed for consistency of outcome analysis, PRRT assessment should be performed 3 months after the last therapy cycle (Q8, Table 1). A

TABLE 2 Distribution of NET experts/Advisory Board Members 2022, responding to the survey according to disciplines.

Faculty	Number of experts	Percentage
Radiology	3	6.5
Nuclear Medicine	4	8.7
Internal Medicine/ Gastroenterology	8	17.4
Endocrinology	12	26.1
Oncology	6	13.0
Pathology/Molecular Biology	5	10.9
Surgeon	8	17.4

TABLE 3 2022 Advisory Board Meeting Attendees' Responses to Theranostics Task Force Survey: Main questions (A) and subquestions (B). Also excluding those entries where no answers were filled.

(A)

Questions	Agree	Disagree	Neutral	Not an expert	Did not answer	Total	Total answered	Agreement total answered (%)	Total no. of experts	Agreement % experts
1	28	10	5	2	1	46	45	62.2	43	65.1
2	32	4	7	2	1	46	45	71.1	43	74.4
3	37	2	6	1	0	46	46	80.4	45	82.2
4	30	1	11	3	1	46	45	66.7	42	71.4
5	31	5	9	1	0	46	46	67.4	45	68.9
6	29	5	8	3	1	46	45	64.4	42	69.0
7	35	3	1	5	2	46	44	79.5	39	89.7
8	39	2	0	3	2	46	44	88.6	41	95.1
9	39	3	1	2	1	46	45	86.7	43	90.7
10	40	1	4	1	0	46	46	87.0	45	88.9
11	38	0	7	1	0	46	46	82.6	45	84.4
12	14	5	19	6	2	46	44	31.8	38	36.8
13	17	6	14	5	4	46	42	40.5	37	45.9

(B)

Questions	PET	CT/MRI	Both	Did not answer	Total	Total answered	% of total answered
7a	10	16	9	11	46	35	28.6
8a	14	15	10	7	46	39	35.9
9a	16	11	11	8	46	38	42.1

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

slight majority (62%) preferred using both CT (and/or MRI) and SST PET (Q8a, Table 1). Additionally, the participants agreed that patients treated with PRRT with equivocal progression (based on ambiguous lesion or nontarget lesion) on CT/MRI should be examined subsequently again for confirmation of PD, preferentially by using both conventional cross-sectional imaging as well as SST PET (Q9, 9a, Table 1). Further, 74% of the participants considered it useful to assess a possible pseudo-progression and delayed response by combining SST PET with diagnostic CT or MRI (Q2, Table 1).

Sixty-five percent of participants supported using SST PET/CT in the response assessment of PRRT (Q1, Table 1). Seventy-two percent agreed that when selecting target lesions on SST PET/CT, not only the intensity of uptake but also its heterogeneity should be considered (Q4, Table 1). Sixty-nine percent agreed that if target lesions in liver, lymph nodes, primary tumor, or other visceral organs showed SST heterogeneity, they should be documented and followed closely (Q6, Table 1).

As to the statement on parameters of potential use for the development of new response evaluation criteria for PRRT, participants agreed that maximum standard unit value (SUV), tumor-to-background ratio (TBR), tumor change in attenuation (HU, analogous to the Choi Criteria), total tumor burden either alone or in combination with novel serum or molecular markers are parameters of moderate to high interest for future studies (Q10, Table 1).

Importantly, 63% of participants did not agree on including unconfirmed PD as a subset of response in SST PET/CT-based response evaluation criteria (Q12, Table 1). Also, 54.1% did not consider tumor growth rate (TGR) measured on CT or MRI for prediction of response to PRRT (Q13, Table 1).

4 | DISCUSSION

PRRT is currently indicated for the treatment of inoperable or metastatic NETs [18,19]. Appropriate baseline staging and evaluation of response to PRRT between treatment cycles (interim response assessment after the second or third cycle) or after the completion of all PRRT cycles are crucial components in the management of NET patients [16]. Although response assessment is commonly recommended to be performed using RECIST criteria, they are not routinely applied in clinical practice. The choice of imaging modality for response assessment is influenced by several factors, including the sites of disease manifestation at baseline and the potential sites of new metastases, similar to therapy monitoring in other systemic treatments for NENs. In Stage IV NET, 80% of patients have liver metastases, and nearly 20% of lesions are located outside the abdomen. While dedicated liver MRI is superior for hepatic staging, SST PET/CT provides highly sensitive and specific whole-body staging and offers the possibility of integrated, fully diagnostic contrast-enhanced

CT. Evidence suggests that patients can be classified into different response categories based on morphological or SUV-based criteria [16]. Whereas the predictive and prognostic relevance of liver metastases in NET is well-studied for systemic therapies, the relevance of extrahepatic metastases is not. There are several reasons for this, among them limited diagnostic accuracy of CT, the most often used staging modality for hepatic and extrahepatic lesions, and lack of sufficient data on standardized response evaluation criteria for PRRT using SST PET/CT are the two most important factors. Since the issue of response assessment if still unresolved, considering that PRRT is a Food and Drug Administration/European Medicines Agency-approved treatment option for NET, definition of standardized criteria of response is required. For this reason, a survey on these issues was promoted by ENETS to collect the real-life expertise of colleagues who are highly involved in NET management, mostly coming from large volume centers. Importantly, survey respondents were primarily clinicians involved in the management of NET patients rather than imaging specialists who might be perceived as having vested interest in promoting their preferred modality.

In general, the results of the survey demonstrate the complexities of PRRT response assessment. There are various perceived, accepted, and proven reasons for this complexity. Among them, the most dominant factor in this regard is the selection of the appropriate target lesion. PRRT is a biologically targeted therapy that primarily operates through direct binding of the therapeutic radiopharmaceutical to SST expressed on the tumor. Consequently, a significant majority of survey participants (72%) agreed that the selection of target lesions should be guided by SST PET/CT imaging. However, choosing target lesions should not only consider the intensity of SST expression, but also the heterogeneity of SST expression. Approximately 69% of participants endorsed this approach, reflecting a broad acknowledgment of the importance of SST heterogeneity, although methods for its assessment remain largely unvalidated. Heterogeneous SST uptake has been identified in multiple studies as an independent adverse risk factor, associated with more aggressive tumor behavior, including treatment resistance and the development of metastases. [20]. Recently, somatostatin receptor antagonists have been shown to be more sensitive and specific in detecting the disease. Some prior studies have shown the predictive and prognostic relevance of SST heterogeneity using visual [21] or quantitative methods [22]. The specificity of SST PET is also useful in the selection of target lesion in the presence of necrotic tumor lesions, previously treated disease, and incidental or multiple secondary malignancies unrelated to NET. The latter is of particular concern, as prior studies have shown that a second cancer can arise in a considerable proportion of NET patients ranging between 10% and 20% [22–24]. Moreover, conventional cross-sectional imaging often faces challenges in differentiating non-malignant lymph node enlargement and indolent lymphomas from lymph node metastases, complicating staging and follow-up when CT, MRI, or PET are used in isolation for target lesion selection. Target lesions with high SST expression have a higher likelihood of responding well to PRRT, sometimes leading to central necrosis or increase in size immediately after therapy due to secondary edema. This relatively rare phenomenon of pseudo-progression, where tumor size may increase due to treatment-related inflammation or necrosis rather than true disease progression, has been well documented, especially when imaging is performed between PRRT cycles or soon after the final cycle [16].

Although assessment of response during PRRT cycles is not yet standardized, the majority of the participants agreed that interim staging should be performed after the second or third cycle. However, 20%–30% of patients may still show disease progression after PRRT. Differentiation of pseudo-progression from real progression, especially in clinical trials, is essential, not only to prevent unnecessary additional treatment cycles, but also to prevent premature PRRT discontinuation. The choice of modality for interim staging was not clear from the outcome of the survey, but there is a strong scientific rationale to preferentially use SST PET/CT, because of its specificity in differentiating tumor necrosis, pseudo-progression versus true progression [25]. A more recent study indicated that interim response assessment can be effectively performed using post-therapy single-photon emission computed tomography (SPECT/CT) [26]. This approach offers several advantages, particularly with advancements in new SPECT scanners, including lower costs and seamless integration into standard care workflows. Notably, Yadav's study demonstrated that SPECT/CT guidance influenced treatment planning in 27% of cases, reducing the standard four therapy cycles to two based on interim findings. Furthermore, a second study suggested that post-therapy SPECT/CT can assess radiation doses delivered to residual tumor sites, potentially guiding decisions on subsequent treatment cycles [27]. Additionally, a third study indicated that it may offer prognostic information by providing insights into overall survival outcomes [28]. While SPECT/CT is not universally available or widely adopted, it remains a valuable modality for evaluating early response or progression during PRRT and optimizing patient-specific treatment strategies. Alternatively, wherever feasible and appropriate, contrast-enhanced CT should be considered together with PET/CT, as it increases the diagnostic performance of PET and the precision of tumor measurements [29]. As NETs treated with PRRT generally are slow-growing tumors, patients achieving stable disease or mild disease progression at 3 months post-last PRRT cycle may convert into partial remission at 6 months or later time point imaging (NETTER-1 paper) [11]. A previous SNMMI guidance report has indicated that, due to the absence of responses in conventional imaging and the occurrence of delayed responses, SST PET should be conducted 9–12 months after the completion of PRRT to establish new baseline imaging data for future comparison [29]. At the time of this survey, the results of the NETTER-2 trial [30] had not been published. Not unexpectedly, given the greater radiosensitivity of more rapidly proliferating tumors, the objective response rate (ORR) by RECIST was substantially higher in NETTER 2, which included G2 and G3 NETs, than in NETTER 1, which predominantly involved G1 NETs (ORR: 43% vs. 18%, respectively). In patients with unequivocal progression on CT at 3 months, especially in NET with Ki67 >10%, SST PET/CT should be used to correctly stage the disease status [31]. The higher likelihood of clonal heterogeneity in patients with higher-grade NETs can

often lead to lesions with low or no SST expression [32]. Hence, it is recommended to combine SST PET with contrast-enhanced CT or MRI, when clinically feasible [33]. Whenever there is concern for liver metastases, contrast-enhanced MRI (preferably with a hepatocyte-specific contrast medium) should be chosen over contrast-enhanced CT [34]. The pros and cons of using SST PET/CT or PET/MRI-based response evaluation criteria in comparison to CT or MRI alone are highlighted in Table 4.

In addition, different affinity profiles of several radiotracers, agonists, or antagonists can complicate the response assessment of PRRT using SST PET. The most commonly used chelator-peptides for SST imaging are agonists: DOTATOC, DOTATATE, and DOTANOC, which all have high affinity for SST subtype 2 but varying affinity for SST subtypes 3 and 5 [35,36]. However, it has been shown that the expression of SST subtype 2 is many-fold higher than that of subtypes 3 and 5 [37], and therefore, the impact is possibly not of major importance. Nevertheless, and in particular when making quantitative readouts (SUV_{max}), it is recommended whenever possible to use same SST PET tracer for response assessment of PRRT [38].

As previously indicated, it is crucial to recognize that surveys, such as the one we conducted, can be subject to various limitations. These include potential biases (such as nonresponders, sampling, social desirability, and recall biases), reliance on self-reported data, dependence on the validity of responses compared with institutional practices, and challenges in accessing certain population groups [39]. In addition, expert opinion manuscripts have several limitations, including subjectivity, potential conflict of interest, and lack of systematic research [40,41].

TABLE 4 Relevant aspects of response assessment criteria using somatostatin receptor PET/CT or PET/MRI versus CT or MRI alone. The statements below, were not part of the survey, were developed during the discussion among Theranostics task force NET experts and are applicable for well-differentiated GEP NET patients treated with PRRT.

SST PET/CT or PET/MRI	CT and/or MRI
Less commonly used	More commonly used
Not yet standardized	Standardized
Visualizes the presence or absence of PRRT target on a cancerous lesion	Cannot visualize the PRRT target present in cancerous lesions
Easier to quantify target expressing total tumor burden	Difficult to quantify total tumor burden
Can better differentiate true progression from radiation necrosis in a cystic/partially necrotic lesion	Difficult to differentiate between radiation necrosis and true progression in a cystic/partially necrotic lesion
Nontarget lesions are better characterized due to higher sensitivity and specificity	Nontarget lesions may be underestimated or falsely characterized due to lower sensitivity and specificity for lymph nodes and bone metastases.

Abbreviations: CT, computed tomography; GEP, gastroenteropancreatic; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SST, somatostatin receptor.

4.1 | Future directions

In general, all survey participants agreed on the clinical need to define response assessment criteria for PRRT that more accurately reflect disease behavior. The maximum standardized uptake value (SUV_{max}) of target lesions can help quantify the density of SST expression [42]. Although receptor–ligand binding for agonistic peptides can theoretically be influenced by several factors, such as receptor saturation, internalization rate, perfusion, peptide concentration, and tumor sink effect, it has nonetheless proven to be a reliable marker for SSTs. In line with this, a study in high-grade NET has shown a close correlation between quantitative gene expression of SST subtype 2 and SUV_{max} of SST PET [43,44]. The effect of carrying doses of octreotide mass on measured SUVs has been studied previously [45]. Use of long-acting somatostatin analogs can also impact SUV assessments [46]. For antagonists, Virgolini et al. demonstrated that neither peptide concentration nor administered injected activity radioactive dose seems to influence SUV_{max} [47]. Ilan et al. have shown that the TBR of ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC are reliable predictors of SST density [48]. In a retrospective clinical study, changes in the TBR between ^{68}Ga-DOTATOC-PET/CT, performed at baseline and following PRRT, correlated to both PFS and overall survival, indicating its feasibility for therapy monitoring, at least for PRRT [49]. Realizing the limitation of SST density alone as predictor and prognosticator of response to PRRT, Zwirtz et al. developed new response evaluation criteria combining tumor attenuation (Hounsfield Unit, HU) and tumor uptake (SUV), coined as ZP criteria by the authors, showed that ZP was useful in predicting disease progression after three cycles of PRRT [16]. Tumor growth rate has a role as a prognostic factor when measured at baseline, and at 3 months after treatment initiation [50]. Changes on TGR while on treatment can also reflect an anti-tumor effect of systemic therapies, including PPRT [51] as also shown by Prasad et al. in a multicenter study, albeit with low number of patients and lesions [52]. Some of the imaging parameters that are relevant for the response assessment of PRRT are highlighted in Table 5. The relevance of these parameters was discussed in post-survey meetings of the theranostics task force.

Although still controversial and not routinely used in the assessment of NET, FDG PET can provide complementary characterization of tumor sites. An increasing likelihood of FDG-avidity is observed as tumor grade increases and has adverse prognostic implications. The concept of spatially concordant and discordant FDG-avid disease has been codified in the NETPET score wherein the ratio of intensity of uptake of SST tracers and FDG are rated from 1 to 5 with 1 representing exclusively SST expression and 5 representing FDG-avidity without SST expression [6]. The latter has been shown to have highly adverse prognostic implications, and perhaps more importantly, identifies lesions that are very unlikely to respond to PRRT. Mixed response to treatment with stability or regression in most lesions, but

TABLE 5 Relevant imaging-based parameters for PRRT, level of interest, and their potential application as predictive or prognostic markers based on current evidence.

Parameters	Predictive or prognostic	Reference	Interest level
SUV_{max} tumor-to-blood ratio	Predictive	[53]	High
Somatostatin receptor heterogeneity	Predictive and prognostic	[21]	High
Somatostatin receptor-expressing tumor burden on SST PET	Predictive	[54]	High
Glucose metabolism on FDG PET	Predictive and prognostic	[55]	High
Tumor growth rate measured on CT or MRI	Predictive	[56]	Moderate
ADC on MRI	Prognostic	[57]	Low to moderate
Tumor perfusion	Prognostic	[58]	Low to moderate
Combining PET and CT parameters	Predictive and prognostic	[42]	Moderate to high

Abbreviations: ADC, apparent diffusion coefficient; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SST, somatostatin receptor; SUV_{max}, maximum standard unit value.

progression in others can reflect the presence of phenotypic variability. Further prospective data are required to ascertain the complementary role of FDG PET/CT in monitoring response to PRRT.

In addition to imaging biomarkers, the response assessment of PRRT may benefit from the inclusion of liquid biopsies that investigate tumor clonal evolution and acquired resistance. In a recent prospective study involving 61 patients with metastatic gastroenteropancreatic NETs, the PRRT prediction quotient (PPQ) was identified as a predictive marker for response, and the NETest levels were elevated in patients who did not respond to ^{177}Lu-DOTATATE [59]. Further research in this area is warranted to enhance our understanding and improve response evaluation in PRRT.

There are several ways to create new response evaluation criteria for PRRT. Utilizing a pre-existing platform for RECIST 1.1 and integrating new imaging parameters for the definition of progression and response is one of the most practical ways of moving forward. The timing of response assessment after PRRT cycles also needs to be standardized. Composite response assessment parameters can be developed by integrating morphological response with clinical, biochemical, and blood-based markers.

Further investigation in a real-world setting is needed to establish thresholds for better characterization of ambiguous lesions, new lesions, and lesions showing pseudo-progression on CT using SST PET. Tumor burden measured on SST PET, complemented by discordant tumor volume when feasible [60], can be integrated into future prospective clinical trials to validate their robustness and practicability. Quantifying the whole tumor volume, such as expressing SST or showing FDG uptake, offers a potentially more accurate method for assessing tumor biology compared to SUV-based parameters, which are often assessed on single lesions. While the predictive and prognostic relevance of quantitatively estimating SST-positive tumor volume in patients treated with PRRT has been explored, these studies have primarily been conducted in single-center settings [61–63]. Real-world data can be generated from radiologists using CT and/or MRI for response assessment to understand the implication of selection of target lesions based on SST PET. The predictive and prognostic values of SST heterogeneity should be assessed further in multicenter prospective and retrospective studies. Novel approaches, including diffusion-weighted MRI and texture feature analyses of CT/MRI and PET images, hold promise for optimizing response assessment to PRRT [64]. However, these techniques remain largely experimental and lack full standardization, preventing their routine clinical use [57,65–67]. Additionally, CT and MRI do not provide information on changes in SST expression on NET cells.

In light of the results of the current survey, which highlight the importance and challenges of accurate response assessment in PRRT, the ENETS Theranostics Task Force has launched a Delphi-based international survey as part of a broader multinational effort to develop a standardized framework for the use of SST PET/CT in evaluating NET responses.

5 | CONCLUSIONS

This survey demonstrates that clinicians remain conservative in moving away from conventional imaging as the preferred method for assessing response to PRRT, despite an increasing openness to integrating molecular imaging for lesion to measurement. A significant impediment to the routine use of SST PET/CT in clinical trials and treatment decisions is the lack of standardized response criteria for this modality. Ideally, addressing clinically relevant questions would involve collecting robust scientific data to provide definitive solutions. The heterogeneity and rarity of NETs, combined with their typically slow-growing behavior, are often cited as challenges limiting research in this area. Over 20 years after the introduction of PRRT, determining how to best assess response remains an unmet need. During this period, we have witnessed the rise of hybrid imaging modalities, with PET/CT becoming the gold standard for assessing PRRT eligibility and the use of combined radiopharmaceuticals to evaluate tumor biology and heterogeneity. Differences in trial design, imaging modalities to assess response (both morphological and PET/CT) based on local practices, technological improvements, reconstruction algorithms (resulting in higher accuracy of novel tomography), and follow-up schemes have contributed to the current lack of standardized

response criteria supported by robust scientific evidence. From a clinical perspective, addressing how to assess response to PRRT is crucial. Agreeing that incorporating molecular imaging as part of response assessment in future prospective theranostics trials is essential to enable assessment and validation of molecular parameters, and perhaps to help define response criteria, will be a vital step forward. As we continue to advance NET therapies, the insights from this survey will be instrumental in enhancing response evaluation strategies for PRRT and optimizing patient outcomes. Collaborative efforts and research endeavors are essential to tackle the complexities of response assessment and pave the way for more tailored and effective PRRT management protocols.

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Vikas Prasad: Conceptualization; methodology; supervision; writing – original draft; writing – review and editing; investigation; data curation. **Anna Koumarianou:** Writing – original draft; writing – review and editing; investigation; methodology. **Timm Denecke:** Writing – review and editing; formal analysis; data curation. **Anders Sundin:** Writing – review and editing. **Christophe M. Deroose:** Writing – review and editing; formal analysis. **Marianne Pavel:** Writing – review and editing; project administration. **Emanuel Christ:** Writing – review and editing; data curation. **Angela Lamarca:** Investigation; writing – review and editing. **Martyn Caplin:** Investigation; writing – review and editing. **Justo P. Castaño:** Writing – review and editing; methodology; data curation. **Clarisse Dromain:** Writing – review and editing; methodology; validation. **Massimo Falconi:** Methodology. **Simona Grozinsky-Glasberg:** Writing – review and editing; methodology; formal analysis. **Johannes Hofland:** Writing – review and editing. **Ulrich Peter Knigge:** Writing – review and editing; data curation. **Beata Kos-Kudla:** Writing – review and editing; formal analysis. **Balkundi A. Krishna:** Writing – review and editing; formal analysis. **Nicholas Simon Reed:** Writing – review and editing; data curation. **Aldo Scarpa:** Writing – review and editing. **Rajaventhan Srirajaskanthan:** Writing – review and editing; validation. **Christos Toumpanakis:** Writing – review and editing; formal analysis. **Andreas Kjaer:** Writing – review and editing; validation. **Rodney J. Hicks:** Conceptualization; methodology; data curation; writing – review and editing; writing – original draft; project administration; supervision. **Valentina Ambrosini:** Conceptualization; methodology; data curation; supervision; writing – original draft; writing – review and editing; validation; formal analysis.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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