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Molecular Imaging for Response Assessment of Neuroendocrine Tumors (NET)

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Assessing treatment response in neuroendocrine tumors (NET) remains a significant challenge due to their typically indolent growth and heterogenity, the frequent occurrence of disease stabilization rather than tumor shrinkage after therapy, and the inherent limitations of conventional imaging criteria. While molecular imaging—primarily somatostatin receptor (SST) PET/CT—has improved lesion detection, the absence of standardized response criteria limits its clinical utility and prevents its use as full replacement of conventional imaging. Emerging strategies, including revised thresholds for dimensional changes, criteria evaluating different features, such as lesions' density and functional tumor volumes, offer potential improvements in response evaluation but require further validation for routine clinical implementation. This review examines the current challenges in assessing NET treatment response, evaluates the strengths and limitations of available imaging modalities, and discusses emerging approaches and future directions for optimizing therapeutic monitoring in the heterogeneous panorama of NET.

Introduction

Neuroendocrine neoplasms represent a diverse group of malignancies with distinct biological and clinical characteristics, encompassing neuroendocrine tumors (NET), well differentiated and generally slow-growing, and neuroendocrine carcinomas (NEC), aggressive and high-proliferating.[1]

According to the latest 2022 WHO classification, NET are graded based on the Ki-67 proliferation index into G1 (<3%), G2 (3%-20%), and G3 (>20%), while NEC are inherently high-grade (Ki-67 > 20%, typically >55%).[1] This grading system serves as a prognostic tool, with higher grades correlating with poorer outcomes.

NET can be further classified as functioning, if they retain secretory activity, or as nonfunctioning, often discovered incidentally or due to symptoms caused by tumor mass effects, with clinical presentation depending on the site of origin and functional status. They can develop throughout the human body, most commonly occurring in the gastro-entero-pancreatic tract (GEP-NET).[2] Pancreatic and colorectal NET are associated with a less favorable prognosis compared to small bowel NET. The incidence and, particularly, the prevalence of NET are rising, likely due to earlier diagnosis and advancements in treatment strategies that have improved survival rates.[3]

The management of NET primarily relies on targeting somatostatin receptors (SST), for both therapeutic and diagnostic purposes.[4,5] Molecular imaging with SST positron emission tomography with computed tomography (PET/CT), that is, PET/CT using 68Gallium-labelled DOTA-peptides radiopharmaceuticals (SST PET/CT) is the gold standard functional imaging technique to demonstrate SST-status: SST PET/CT is recommended for NET staging, restaging, identification of the unknown primary tumor and for selecting candidates for peptide receptor radionuclide therapy (PRRT).[6,7]

PRRT with [177Lu][Lu-DOTA0-Tyr3]octreotate ([177Lu]Lu-DOTATATE) is currently recommended in Europe for

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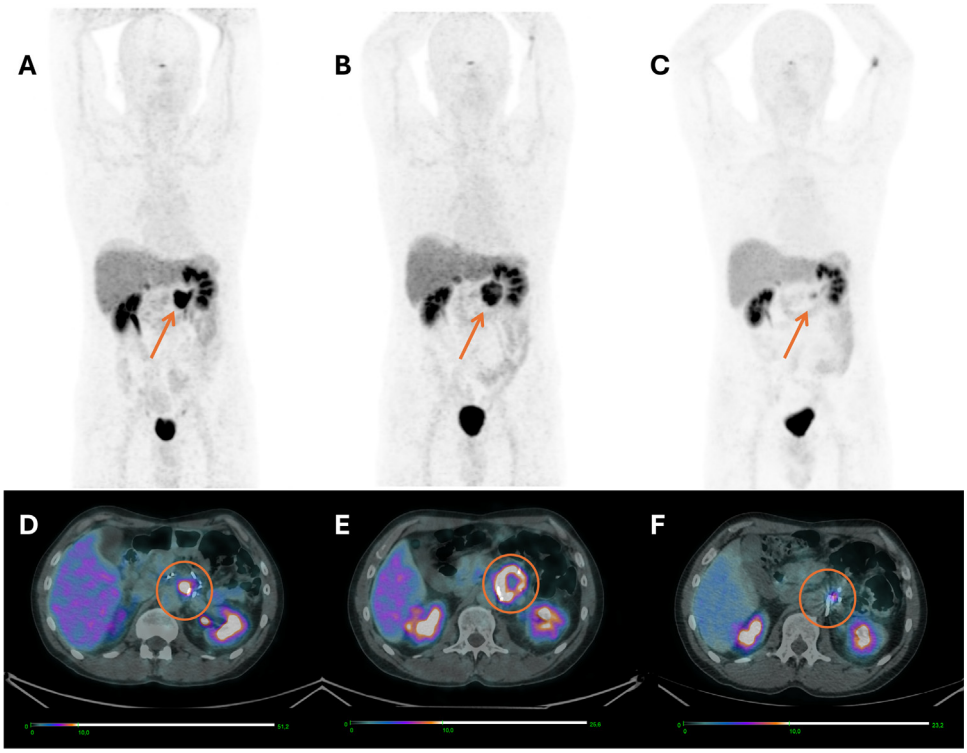

Figure 1 Maximum-intensity projection (A, B, C) and fused (D, E, F) images from consecutive [^{68}Ga]Ga-DOTANOC PET/CT scans of a patient with local relapse of a pancreatic G2 NET (Ki-67: 3%) treated with PRRT, which resulted in disease control for nearly a year (A, D). A restaging PET/CT scan showed disease progression due to an increase in the size of the abdominal lesion, presenting with necrotic changes (B, E). Consequently, CAPTEM therapy was initiated, leading to a subsequent reduction in lesion size and SST-uptake (C, F).

patients with unresectable or metastatic, G1 or G2, SST-positive GEP-NET that have progressed to somatostatin analogues.[8] In USA eligibility criteria for the treatment of SST-positive GEP-NET are broader, including the foregut, midgut, and hindgut neuroendocrine tumors in adults[9]; more recently (2024), it was also FDA-approved for treatment of NET in children >12 years old. The NCCN Guidelines also recommend consideration for PRRT in well differentiated lung NET and in pheochromocytomas and paragangliomas.[10]

Unlike many other malignancies, NET often exhibit an indolent biological behavior, posing unique challenges in assessing response to therapy. Their heterogeneity—spanning from different primary sites, clinical features, histological grades, and functional statuses—complicates management and necessitates tailored approaches to diagnosis and treatment. Moreover, with the expanding of treatment options over the past few decades, the optimal strategy for response assessment remains unclear, since the expected effects of each therapeutic approach may vary.

Most treatment options often result in disease stabilization rather than significant tumor size reduction, and from a clinical perspective the most relevant issue is to identify progressing patients. However, the treatment goal may differ depending on the clinical scenario: for example, while resectable localized non-functional NET may be treated with curative-intent surgery, metastatic functional NET patients need to control both disease burden and excessive hormone production that strongly impacts the quality of life (eg, gastrin-releasing tumors may cause Zollinger-Ellison syndrome, while serotonin-secreting tumors can be responsible for carcinoid syndrome with diarrhea, flushing, abdominal pain). In these latter functioning cases, achieving symptoms control is crucial and an indirect measure of response to treatment, even if tumor size remains unchanged. In other cases, more aggressive tumors treated with chemotherapy may shrink in response to treatment (Fig. 1).

Considering the inherent biological differences among various forms of NET and treatment options, there is no consensus on the optimal treatment response strategy.

Although Response Evaluation Criteria in Solid Tumors (RECIST 1.1 in the latest version) were developed to standardize the assessment of dimensional changes in solid tumors, primarily for clinical trials,[11] both morphological and molecular imaging procedures are routinely employed in the setting of neuroendocrine tumors. However, the former has inherent limitations, while the latter lacks standardized response criteria.

This article aims to outline the key challenges associated with response assessment in NET and provide an overview of potential future directions.

Morphological and Molecular Imaging: Strengths and Weaknesses

Cross-sectional imaging techniques used for both the initial evaluation of NET and response assessment include

morphological imaging, specifically contrast-enhanced computed tomography (ceCT) and MRI ("Conventional imaging"), and functional imaging, primarily SST PET/CT, which has largely replaced SST scintigraphy (OctreoScan) for evaluating SST-status.

CeCT represents the standard method for dimensional measurements, as well as for evaluating lesion density and contrast-enhancing patterns. NET are typically hypervascular, exhibiting marked arterial-phase enhancement, followed by contrast wash-out in the portal venous phase, where they appear ISO- or hypodense compared to surrounding tissues. High-grade, less differentiated NET, tend to display low enhancement due to the presence of necrosis and fibrosis (both of which can challenge CT-based response assessment). The sensitivity of CT in NET detection is 61-93%, and the specificity is 71%-100%.[6,12]

MRI can be useful in equivocal situations, most commonly for the assessment of pancreatic and hepatic parenchyma when small lesions (measuring less than 1 centimeter) are suspected. NET appear hypointense on T1-weighted images, hyperintense in T2- and diffusion-weighted imaging (DWI), and hypointense on apparent diffusion coefficient (ADC) maps.[12]

Endoscopic ultrasound is commonly used to diagnose and characterize rectal, gastric, duodenal, and pancreatic NET, as well as for staging bronchial NET, and enables tumor sampling for histopathological evaluation. Contrast-enhanced ultrasonography is employed for the assessment of liver, particularly in equivocal cases or intraoperatively; however, it is not routinely used for response assessment.

SST PET/CT has been demonstrated to show a very high accuracy in SST-expressing tumor lesions, frequently outperforming diagnostic-CT both at primary and metastatic sites.[13,14]

The sensitivity of SST PET/CT for detecting NET disease is 92% (with a range of 64%-100%), while its specificity is 95% (with a range of 83%-100%).[6]

The accuracy of each imaging modality, including both morphologic and functional imaging, is variable also depending on the anatomical site and size of the lesions being evaluated.

Conventional imaging techniques may demonstrate suboptimal performance in identifying the primary tumor's site when the diagnosis is established after the detection of metastatic disease, particularly in case of small bowel tumors, which may be multifocal (for this reason, the palpation of the entire small bowel during surgery is always recommended).[15] SST molecular imaging has demonstrated higher accuracy in detecting cancers of unknow primary compared to ceCT.[16]

Common sites of metastatic spread in NET include lymph nodes, bone, and liver.[17] Centimetric or over-centimetric hepatic lesions can be effectively measured using ceCT, while MRI may be helpful in evaluating smaller lesions.

SST PET/CT liver assessment is hampered by the physiological biodistribution of the radiolabeled-SST-analogs, while novel experimental radiolabeled-SST-antagonists have demonstrated superior performance at this level as they exhibit lower physiologic hepatic uptake.[18] Moreover, liver uptake is reduced in patients undergoing somatostatin analog treatment.[19]

Bone lesions can be challenging to assess using ceCT (with a sensitivity of 61%, ranging from 46 to 80%[6]) and they are not considered as target lesions in RECIST 1.1 criteria, unless a soft tissue component is present. In contrast, SST PET/CT demonstrates high accuracy for the evaluation of bone lesions, both for lesions >1 cm and <1 cm, even in cases without a morphologically evident alteration on ceCT.[20,21]

In addition, necrotic lesions, pleural effusion, ascites, peritoneal carcinomatosis and leptomeningeal disease are non-measurable according to RECIST 1.1 and cannot be classified as target lesions.

One of the most widely recognized advantages of functional imaging over conventional imaging is its ability to detect small lesions at very early stages, even before morphological alterations occur: this is particularly relevant for bone involvement, small lymph nodes (given that only nodes with a short axis >15 mm are considered pathologic on CT) and peritoneal metastases.[15]

Despite these advantages, molecular imaging is not yet suitable as a full replacement for morphological imaging, primarily due to the lack of well-defined and standardized criteria for SST-PET objective response evaluation. The extent of radiotracer uptake cannot be directly equated to morphological dimensions, as the uptake area is influenced not only by lesion size but also by intensity—a phenomenon known as the "partial volume effect." This effect can vary over time regardless of response, and depending on multiple factors, including variability/heterogeneity in SST-expression, radiolabeled SST-analog used for PET/CT imaging, tracer injected activity, uptake times, camera technology, and methods used for image reconstruction.

Currently, several different radiolabeled SST-analogs are employed for PET/CT diagnostic imaging: the FDA approved the use of [68Ga]Ga-DOTATATE (2016), [68Ga]Ga-DOTATOC (2019), [64Cu]Cu-DOTATATE (2020), while the EMA approved the use of [68Ga]Ga-DOTATOC (2016). More recently, [68Ga]Ga-DOTANOC entered the European pharmacopoeia (11.3) (2024). Despite differences in SST-subtypes binding, these radiopharmaceuticals are considered clinically equivalent, although direct comparison of functional parameters (eg, SUVmax, SUVmean, ratios of lesion to liver or spleen, receptor-expressing tumor volume) between different tracers is not recommended. In fact, while reductions in SUV correlate with response when using FDG for the response assessment of onco-hematologic tumors, this is not always true when using radiolabeled-SST analogs: SST SUV reduction may be due to a decrease in lesion size, but it could also result from dedifferentiation (loss of SST expression). For these reasons, the variation in semi-quantitative parameters alone is not considered a reliable biomarker for response assessment.[22,23]

In contrast, the appearance of new findings at sites compatible with NET secondary lesions, with or without a

corresponding alteration on the CT-component, is more confidently interpreted as progressive disease (PD).

RECIST Criteria in Clinical Trials and Clinical Practice

Current guidelines recommend the use of RECIST 1.1 for NET response assessment, although they are not routinely used in clinical practice.[6] Moreover, considering the well-known limitations of RECIST and the potential advantages of SST PET/CT, most expert consensus support the combination of both SST PET/CT and ceCT for NET response assessment.[24,25]

The common challenge shared by both molecular and conventional cross-sectional imaging is the difficulty in depicting the behavior of slow-growing neoplastic cells, especially since long-term stabilization is the most frequently expected treatment outcome in responding patients with well-differentiated NET.[26]

In real-world clinical practice, RECIST criteria are considered time-consuming and are not widely used outside of the clinical trial setting.[27] Moreover, routine clinical interpretation may differ from RECIST assessment: in a recent publication, authors observed disagreement between RECIST 1.1 and the routine clinical read in approximately one-third of cases in patients enrolled in solid tumor clinical trials.[28] Most often, clinical reads overcalled PD relative to RECIST (32%). Discordant reads were mostly due to errors in lesion measurement (insufficient increase in the sum of lesion diameters, <20%) or the assessment of a single target lesion, as well as over-classification of equivocal findings as progression (including both new lesions or non-target lesions). On the contrary, PD was underdiagnosed in a limited number of cases (3%), likely due to comparison with the most recent assessment rather than with baseline or nadir assessments as required by RECIST 1.1.

However, the relationship between progression and survival is not straightforward, since even patients with advanced disease can still experience prolonged survival after progression. For this reason, there is no clear evidence of how to change management based on oligoprogression, i.e. progression of one to few lesions which may be amenable to local treatment without changing systemic treatment or starting a new therapy.

Progression-free Survival and Overall Survival in NET Trials

The recommended primary endpoint for phase 3 trials assessing novel systemic therapies in NET is progression-free survival (PFS), defined as the time from randomization to radiographic progression using RECIST 1.1, or death from any cause.[29] This recommendation is primarily based on feasibility reasons, given the challenges associated with the long follow-up periods required to reach the overall survival (OS) endpoint in NET trials. Moreover, because NET generally exhibit an indolent behavior, patients may be able to receive several different lines of treatment in the course of their disease. As such, the administration of subsequent treatments in patients who progress during clinical trials, either through cross-over or outside the trial, may interfere with OS, making it an unreliable endpoint for evaluating treatment efficacy.

This was observed in several randomized, placebo-controlled phase III trials, like the PROMID, CLARINET, and the sunitinib studies, where the experimental arm showed a benefit solely in terms of PFS.[4,30,31]

In the RADIANT-4 trial of everolimus vs placebo in patients with advanced lung or GEPNET, OS was a key secondary endpoint. While everolimus exhibited a trend toward improved OS compared to placebo, the difference did not reach statistical significance, likely due to contamination in the placebo arm after progression and study unblinding.[32]

Similarly, according to the final results of the NETTER-1 trial, the benefit of [177Lu]Lu-DOTATATE over octreotide LAR in terms of median OS was not statistically significant (48 months vs 36.3 months, respectively), primarily due to the high rate of cross-over. On the contrary, when adjusted for cross-over, the median OS in the control arm was 30 months.[33]

Therefore, the use of PFS as a surrogate for overall survival (OS) in NET has been debated due to the lack of direct evidence demonstrating the validity of this principle.

Addressing this issue, Ter-Minassian et al. conducted a retrospective study on large cohorts of patients with advanced NET treated with somatostatin analogs (n = 440) and everolimus (n = 109): in both cases, PFS significantly correlated with OS. The median follow-up time for patients treated with single-agent SSA was 7.1 years, median PFS was 17 months, and median OS was 6.4 years. A landmark analysis excluding patients who died before progression (ie, death not included in the PFS definition) confirmed the association between PD and OS.[34]

Other studies, albeit retrospective, supported the association of PD, as defined by RECIST criteria, with OS.[35,36]

The CABINET (Cabozantinib vs placebo, NCT03375320) and COMPETE ([177Lu]Lu-Edotreotide vs. everolimus, NCT03049189) trials, with OS as secondary endpoints, are still ongoing, and may provide further insights into survival outcomes in the future.

In summary, PFS as defined by RECIST 1.1 seems to correlate with OS according to retrospective studies, although surrogacy has not been formally demonstrated to date.

Objective Response

Since systemic therapies for NET frequently have cytostatic rather than cytotoxic effects, it is difficult to assess the efficacy of therapeutic interventions based on tumor size reduction alone. Multiple trials have shown that NET rarely exhibit sufficient dimensional reductions to meet the RECIST 30% cut-off for partial response (PR), even if benefiting from treatment in terms of PFS.

The RADIANT-3 trial demonstrated the efficacy of everolimus in prolonging PFS compared to placebo (11 months in the everolimus arm vs 4.6 months in the placebo arm) in 410 patients with advanced pancreatic NET. Despite the benefit in terms of PFS, objective response as defined by RECIST1.1 was observed in only 10 patients (ORR: 5%) in the everolimus arm, but also in 4 of the placebo arm (ORR: 2%). Thus, the main effect was RECIST-defined disease stabilization rather than marked tumor shrinkage.[37]

Similarly, in the CABINET trial, which reported improved PFS in patients with advanced pancreatic or extra-pancreatic NET treated with cabozantinib compared to those in the placebo arm, partial responses were observed in 5% of patients in the cabozantinib group (vs. none in the placebo group).[38]

Thiis-Evensen et al.[39] aimed to explore whether achieving an objective response versus stable disease (SD) after treatments like PRRT, chemotherapy, or everolimus impacted survival outcomes in NET patients. Radiological assessments were conducted using ceCT or MRI, with objective response defined as a clear reduction in lesion size (≥1-2 mm) and stable disease as no change in tumor size or number. For PRRT-treated patients, response was also evaluated using RECIST 1.1 criteria. The study found no significant difference in time to progression between patients with objective response and those with stable disease, regardless of the treatment subgroup or assessment method employed.

In the retrospective analysis by Van Vliet et al.,[40] PFS and OS were comparable in patients with objective response and stable disease assessed 3 months after the completion of PRRT using RECIST, SWOG, mRECIST and mSWOG criteria (n = 257 patients). The different criteria showed good correlation.

These data suggest that tumor objective response rate alone may not be an optimal marker to assess treatment activity in NET to the majority of systemic treatments, in lieu of the lack of differential survival benefit in patients achieving an objective response compared to those with stable disease, as defined by RECIST.[31]

Alternative Criteria for NET Response Assessment

Due to the low occurrence of objective responses in NET and their indolent growth pattern, some authors argue that the RECIST-defined thresholds for partial response and progressive disease may not be adequate, suggesting that even smaller changes could be clinically significant.

The Choi criteria were introduced as an alternative to RECIST 1.1 for assessing tumors where changes in density are expected and dimensional variations may be less relevant[41] (Table). According to Choi criteria, the dimensional cut-off for decrease in size is 10%; in addition, a density decrease measured in Hounsfield Units (HU) of at least 15% is a criterion for partial response. The Choi criteria were originally developed for gastrointestinal stromal tumors (GIST) and soft tissue sarcomas and rely on the assessment of the venous phase of the CT. Despite not being designed for NET, they have been investigated for assessing response to PRRT and tyrosine kinase inhibitors.[42] Recently they were used to evaluate a single center cohort of 178 patients with GEP-NET treated with PRRT: Choi criteria classified a higher number of patients as having PD and PR and a lower number of patients as having SD compared with RECIST 1.1.[43]

Table Response Criteria

Response Categories	Criteria			
	RECIST 1.1[11]	**mRECIST**[82]	**CHOI**[41]	**PERCIST**[83]
CR	Disappearance of all target lesions	Disappearance of intratumor arterial enhancement in all target lesions	Disappearance of all lesions	Disappearance of all lesions (with any remaining lesions showing lower metabolic activity than the liver)
PR	≥30% decrease in sum of diameter of target lesions	≥30% decrease in tumor burden per RECIST considering only viable tumor of target lesions (that with arterial enhancement on CE radiological techniques)	A decrease in tumor size by ≥10% or a decrease in tumor density (Hounsfield units) by ≥15%.	≥30 % relative and ≥0.8 absolute decrease in 18F-FDG uptake (SUL peak of target lesion) and no >30 % increase in SUL of nontarget lesions and no PD by RECIST
SD	Does not meet criteria for CR, PR, nor PD	Does not meet criteria for CR, PR, nor PD	Does not meet criteria for CR, PR, nor PD	Does not meet criteria for CR, PR, nor PD
PD	≥20% increase in sum of diameters of target lesions	>20% increase in tumor burden per RECIST considering only viable tumor of target lesions OR Appearance of new lesions	≥10% increase in tumor size and does not meet criteria for PR by tumor density or appearance of new lesions	>30 % relative and 0.8 absolute increase in 18F-FDG uptake (SUL peak of target lesion) or Unequivocal increase in extent of 18F-FDG uptake (75 % in total lesion glycolysis volume with no decline in SUL) or New 18F-FDG-avid lesions

A retrospective study compared RECIST 1.1 and Choi response criteria in a population of 75 patients with GEP-NET. Median PFS was 14 months according to Choi and 15 months according to RECIST. Agreement between the criteria on disease status at the last follow-up was 65%. Statistically significant differences in OS were found between patients with PD and non-PD according to RECIST 1.1 criteria, while OS in PD and non-PD groups assessed by Choi was not significantly different.[35]

Similarly to the results obtained for metastatic renal cell carcinoma.[44,45] Lamarca et al.[46] found that a 10% reduction in marker lesions independently impacted on PFS in patients receiving sunitinib, even when adjusted for other prognostic factors. In addition, the best response to treatment was achieved during the first 7 months of treatment, suggesting the possibility of early identification of patients benefiting from the therapy.

De Mestier et al.[47] retrospectively studied patients with advanced pancreatic or small intestine NET with liver metastasis, without early progression within 6 months after the start of first- or second-line systemic treatments, assessing different cut-offs for the dimensional decrease of the sum of lesion diameters and density changes. A decrease of $\geq$10% in the size of three hepatic lesions significantly predicted prolonged time-to-treatment failure, while response defined by RECIST 1.1 or density criteria did not.

Molecular imaging with SST PET/CT has shown superior lesion detectability compared to conventional imaging, but whether the earlier detection of disease progression translates into improved patient outcomes remains unclear and challenging to evaluate, given the difficulties associated with assessing OS outcomes in NET.[48]

Huizing et al. retrospectively investigated the value of an early response assessment using RECIST 1.1, Choi criteria, and changes in SST status through SST PET/CT in predicting OS in 44 patients receiving PRRT. PD according to RECIST 1.1 and Choi at 9 months was significantly correlated with poorer OS compared to SD (PD vs SD = 27 vs 32 months for RECIST 1.1, 28 vs 37 for Choi). The appearance of new lesions at both morphological and molecular imaging did not significantly impact OS. No associations between changes in [68Ga]Ga-DOTATATE PET/CT semiquantitative parameters and OS were observed.[36]

Zwirtz et al. investigated SST PET/CT parameters in addition to morphological imaging-based criteria. RECIST 1.1, Choi, PET criteria based on EORTC referred to as MORE,[49] and a new ZP parameter (combining HU and SUVmean) were compared to assess PRRT response in 34 patients with NET. RECIST 1.1, Choi, and SUVmax-based response assessments varied significantly. In this study, PET-based criteria showed predictive and prognostic yield: baseline ZP and ZPnormalized best predicted lesion progression after three PRRT cycles; progressive disease after two cycles by MORE criteria correlated with shorter OS, while ZP-based progression showed a similar trend.[48]

In summary, it is unclear to what extent an earlier definition of progression- through lower dimensional cut-offs, tumor density or SST uptake changes, or the appearance of new small lesions (detected either using conventional or molecular imaging) will impact patient's outcome. This issue needs to be addressed through further studies.

Functional Volumes for PRRT Response Assessment

SST PET/CT is mandatory for establishing SST expression-status prior to PRRT to assess eligibility. Beyond patient selection, baseline imaging provides critical predictive and prognostic insights, as higher tracer uptake generally correlates with improved outcome.[50-52] The baseline scan is used as a reference for subsequent response assessment, although there is still no consensus on the standardized PET criteria for image interpretation.

Variations in PET-derived parameters from a single lesion (typically, but not exclusively, the most avid) fail to accurately predict response, likely because they do not represent the total tumor burden. The development of semi-automatic segmentation methods has enabled quantification of the entire SST-expressing tumor burden. Quantitative metrics derived from segmentation include total tumor volume (SST-TV) and total lesion activity (TLA), which is calculated as the sum of the product of SST-TTV by SUVmean of each lesion (therefore also providing indirect data on SST-expression heterogeneity). The selection of the optimal method and thresholds for segmentation is a critical issue, as it directly impacts the accuracy and reproducibility of quantitative measurements. Common thresholding methods for neuroendocrine tumors include fixed values, such as 42% of the lesion's SUVmax, or adaptive thresholds, which are adjusted intra-patient based on the SUV values of the backgrounds (mostly the liver).[53] AI-based approaches may further streamline and improve the segmentation process.[54]

Limitations of the fixed-threshold method include potential underestimation of tumor volume, as PRRT candidates often exhibit very high SUVmax values at baseline. Conversely, using liver background as a lower cutoff may be problematic in patients with extensive liver involvement due to the difficulty of obtaining a region-of-interest of the healthy parenchyma, or with patients with therapy-induced changes in liver background (often due to SSA).[19] A further potential limitation is the need to estimate the SST-TV ensuring reproducible methods, including the same radiolabeled analog, camera technology, and reconstruction algorithm.

Most of the studies conducted so far investigated the volumes prognostic ability: higher FDG tumor volumes were associated with higher grades and more unfavourable outcome.[55] More recently, discordant tumor volume (SST-negative/FDG-positive) was reported as a predictor of poor prognosis in patients undergoing PRRT.[56]

Volume-based methods for response assessment are not yet routine in clinical practice, and few studies have explored their utility in this setting. Moreover, when dealing with tumor volumes, there is no evidence of what thresholds to employ to define SD, PR and PD: commonly used thresholds are based on morphological uni- or bidimensional morphologic assessments, whereas functional volumes are inherently three-dimensional (eg, the same functional volume could correspond to lesions of different sizes).

In a recent retrospective work by Chaban et al., changes in tumor volumes on SST-PET/CT before and after PRRT (typically 4 treatment cycles) in 90 patients recruited at two centers

showed that the highest concordance with PFS was achieved by defining response as a 40% decrease of the tumor volume and progression as a 20% increase in tumor volume. Irrespective of volume changes, prognostic value was improved by defining progression also by the appearance of new metastatic lesions (EANM24, Abstract OP-610- unpublished results).

Another retrospective study of 90 PRRT-treated patients found a median SST-TV reduction of 63% post-treatment, but neither baseline SST-TV nor its decrease correlated with OS.[57]

Mamulashvili Bessac et al. evaluated organ-specific responses to [177Lu]Lu-DOTATATE in a study involving 33 patients with metastatic small bowel NET. Target lesions were identified, and both SUVmax and SST-TV were measured at three timepoints: baseline, mid-treatment, and post-treatment. Objective response was determined based on percentage changes in SUVpeak of the most active lesion, using PERCIST cut-offs. The results showed varying degrees of SUVmax and SST-TV reductions across different anatomical sites: liver metastases showed significant reduction in both SUVmax and SST-TV from baseline-PET and end-of treatment-PET, with early response evident after two PRRT cycles while lymph nodes responded more slowly, primarily during the final treatment cycles. Peritoneal and bone metastases showed a continuous decline in SUVmax, but no significant changes in SST-TV. This suggests that site-specific SST-volume thresholds may be needed to define progression/response. None of the observed changes correlated with PFS, likely due to small subgroup sizes (progressive: $n = 20$; non-progressive: $n = 13$).[58]

Interim Response Assessment to PRRT

Interim response assessment to PRRT, typically performed after two cycles, can be useful for obtaining early information on tumor response to treatment. In fact, it is has been demonstrated that the higher proportion of the cumulative dose to disease sites is delivered with the first treatment.[57]

Identifying responders versus nonresponders can influence the clinical decision-making process, guiding whether to proceed with the remaining cycles, discontinue treatment in cases of progression, or even consider surgery in selected cases of objective response. Local practices vary widely in the schedule of interim assessment.

In the setting of prostate cancer theranostics, SPECT/CT has been proposed to optimize treatment personalization following the observations that an increase in tumor volume between cycle 1 and 2 after [177Lu]Lu-PSMA was associated with worse PFS.[59]

This is particularly relevant in patients at high risk of toxicity and those undergoing PRRT rechallenge. However, the impact of interim evaluations, using SST PET/CT or SPECT/CT, on patient outcomes is still unclear.[36]

Christoph et al. reported the impact of interim evaluation after 2 cycles of PRRT on the continuation of the therapy, using either CT, MRI or SST PET/CT: of 119 patients with GEP-NET, 83 completed all 4 cycles and 36 interrupted the course after the early assessment for PD (n = 27), PR leading to surgery (n = 3), toxicity (n = 5) or death (n = 1).[60]

Durmo at al. retrospectively analyzed 46 patients who underwent PRRT and found that although baseline SST-TV was associated with OS, interim PET performed after 2 cycles was not followed by management changes, questioning the usefulness of this approach.[61]

Instead, Shin et al.[62] observed that basal and interim [68Ga]Ga-DOTA-TOC PET/CT scans, through proportional changes in SST-TV and TLA, effectively predicted PFS in NET patients receiving PRRT (n = 24 patients).

In the prospective phase II LUMEN study, Mileva et al. demonstrated that an early ≥10% reduction in SST-TV on SST-PET/CT following the first PRRT cycle (n = 37 patients) correlated significantly with prolonged PFS (51.3 vs 22.8 months; HR: 0.35, 95% CI 0.16-0.75, $P = 0.003$).[63]

Following each PRRT cycle, post-therapy imaging with planar scintigraphy or SPECT/CT is performed to verify the biodistribution of the administered radioligand, and allow dosimetry calculations. Notably, SPECT offers added clinical value by enabling interim and end-of-treatment response evaluation, without requiring additional radiopharmaceutical administration and may reveal early detection of gross progression, despite its reduced resolution/sensitivity when compared to PET/CT.

The detection of new [^{177}Lu]Lu-DOTATATE-avid lesions, of mismatched lesions (with minimal [^{177}Lu]Lu-DOTATATE avidity but evident on the corresponding non-diagnostic CT component of the SPECT/CT) or of secondary features (eg, ascites) warrants particular attention, given their association of these features with adverse disease outcomes.[64]

In a retrospective study including 100 patients with NET, SPECT/CT mostly showed qualitatively SD during PRRT (80% after cycle 2, 79% after cycle 3, 73% after cycle 4). However, management changes were performed in 27% of cases. Most treatment changes occurred after cycle 2 (33% major, 67% minor) and cycle 3 (62% major, 33% minor). The author reported their subjective decision to interrupt PRRT in 5 patients showing marked response (2 after the second cycle and 3 after the third cycle).[65]

In a recent retrospective study of 51 patients with NET who underwent ≥4 PRRT cycles, a favorable response (PR vs SD according to RECIST) after two PRRT treatments was predictive of achieving PR after completion of the PRRT-course.[66]

The results of the studies investigating the impact of interim assessment are variable, likely hampered by their mostly retrospective design, and mixed cohorts of NET with diverse primary sites and grades that are all known to affect the clinical outcome. Moreover, the only approved schedule of the PRRT course consists of 4 administrations (the allowed changes in injected dose or timings only follow the occurrence of toxicity), therefore scheduled changes based on partial interim response are not performed in clinical practice. Other limitations to the routine use of SPECT/CT and SST PET for interim response assessment in clinical practice are the lack of consensus on the optimal timing, interpretation criteria as well as the aforementioned feasibility of treatment schedule changes outside a clinical trial setting.

Pseudoprogression

Pseudoprogression has been described as a transient increase in lesion size caused by inflammation-induced changes, that is, edema and infiltration of immune cells. This phenomenon is considered rare, mainly because early response assessment is not routinely performed in clinical practice. Indeed, this phenomenon has been described in the literature and needs to be considered when performing interim evaluations.[48,67,68] In the study by Zwirtz et al.,[48] 11% of the lesions that increased in size after the first PRRT cycle, subsequently decreased during the following administrations, configuring pseudoprogression. This occurred in 7/34 patients and in 9/77 lesions analyzed, which increased up to 39% in size before reducing their volume at later assessments. Brabander et al.[68] reported a reversible ≥10% increase in lesion size in 18/354 patients at the first follow-up assessment after the completion of PRRT, all of which finally resulted in SD as the treatment outcome at 6 months. Moreover, 51/54 patients who had PD as the treatment outcome progressed due to the appearance of new lesions rather than due to significant diameter increases according to SWOG criteria. For these reasons, the authors suggest that early true progression is rare and pseudoprogression should be kept in mind when observing early increases in lesion size.

Heterogeneity and Dual Tracer PET/CT

Tumor heterogeneity refers to a variation in tumor biological characteristics within the same patient, or even within the same lesion, when different metastatic foci present with different grades of differentiation/SST expression.[69-71] These differences can be present at the time of the diagnosis or emerge over time. Tumor heterogeneity is considered an unfavorable prognostic factor, as it can result from the selection of aggressive clones (possibly treatment-induced) that ultimately drive progression.[72] Moreover, SST uptake is considered a favorable prognostic factor and SST-low uptake/negativity in NET has been associated with worse survival outcomes.[51,73]

A multicenter study investigated the prognostic value of SST heterogeneity assessed by PET/CT in 141 patients before undergoing PRRT. The authors identified eight prognostic heterogeneity parameters, with the textural feature "Entropy" emerging as a significant predictor of both PFS and OS.[74]

Graf et al. visually assessed the heterogeneity of SST expression in 65 patients treated with PRRT, finding that patients with heterogeneous SST expression, defined by intra-lesional variability in the modified Krenning score in >50% of target

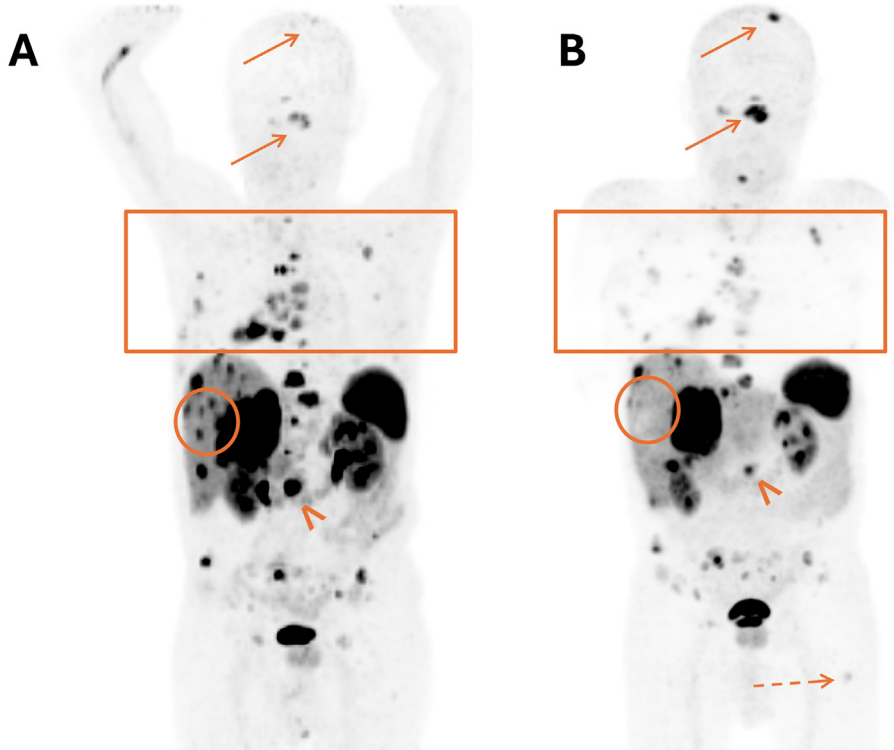

Figure 2 MIP of baseline (A) and end-of-treatment (B) [68Ga]Ga-DOTANOC PET/CT scans of a patient with advanced G2 pancreatic NET (Ki67: 12%), treated with PRRT following progression on somatostatin analogues. The post-PRRT scan showed the disappearance of several hepatic lesions (circles) and a reduction in SST uptake and/or extent in the primary pancreatic tumor (v), as well as in multiple pulmonary, nodal, and bone lesions (boxes). However, two skull lesions showed increased extent and uptake (arrows), and new bone lesions emerged in the pelvis and left femur (dashed arrow). A subsequent scan confirmed PD due to the appearance of new bone and hepatic lesions; chemotherapy with capecitabine and temozolomide was initiated. Heterogeneous SST expression was observed in both the baseline and post-PRRT PET/CT scans.

lesions, had a significantly lower median TTP and OS compared to those with more homogeneous expression.[75]

These results can be explained by the fact that SST-heterogeneous lesions cannot be fully targeted by the cytotoxic radiation, providing a rationale for the reduced responses to PRRT observed in these cases[76] (Fig. 2). Moreover, heterogeneity often underlies dedifferentiation phenomena, with concurrent loss of SST and increased proliferation and, consequently, of metabolic activity, which can be visualized through increased FDG uptake. RECIST criteria may fail to detect dedifferentiation since this process can develop without substantial changes in lesion size. In contrast, SST imaging (standalone or complementary to FDG PET/CT) effectively captures this biological transition (Figure 2). The prognostic yield of FDG PET/CT is well-established,[77-79] prompting the development of various grading scores based on combined SST and FDG PET/CT.[80,81]

For this reason, performing an FDG PET/CT in patients with suspected high SST heterogeneity may provide crucial insights into the extent of dedifferentiation of the whole tumour burden. The utility of these multimodal imaging findings as reliable progression markers warrants additional investigation to assess both impact on outcomes and changes in clinical management.

Conclusion

The search for accurate criteria for treatment response assessment in NET is hampered by their typically heterogeneous biology and slow-growing behavior. Moreover, the studies investigating new criteria for response often portrayed conflicting results, likely reflecting small cohorts of diverse patients. Molecular imaging can provide valuable insights into the biological characteristic of the whole tumor burden. The combination of SST/FDG data provides a non-invasive evaluation of NET heterogeneity. However, the lack of PET standardized criteria for interpretation of functional changes after treatment, does not allow the full implementation of molecular imaging alone for response assessment. Combination of functional and morphological imaging is still crucial to accurately describe treatment response in clinical practice.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Martina Di Franco: Writing – original draft, Conceptualization. **Giuseppe Lamberti:** Writing – review & editing. **Davide Campana:** Writing – review & editing. **Valentina Ambrosini:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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