Somatostatin Receptor Imaging and Theranostics: Current Practice and Future Prospects

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A new era of precision diagnostics and therapy for patients with neuroendocrine neoplasms began with the approval of somatostatin receptor (SSTR) radiopharmaceuticals for PET imaging followed by peptide receptor radionuclide therapy (PRRT). With the transition from SSTR-based γ-scintigraphy to PET, the higher sensitivity of the latter raised questions regarding the direct application of the planar scintigraphy-based Krenning score for PRRT eligibility. Also, to date, the role of SSTR PET in response assessment and predicting outcome remains under evaluation. In this comprehensive review article, we discuss the current role of SSTR PET in all aspects of neuroendocrine neoplasms, including its relation to conventional imaging, selection of patients for PRRT, and the current understanding of SSTR PET–based response assessment. We also provide a standardized reporting template for SSTR PET with a brief discussion.

Key Words: somatostatin; SSTR; peptide receptor radionuclide therapy; neuroendocrine neoplasms; 68Ga-DOTATATE; 68Ga-DOTANOC

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uroendocrine neoplasms (NENs) are rare, heterogeneous, and typically slow-growing, accounting for about 0.5% of all diagnosed malignancies. Originating from the secretory cells of the neuroendocrine system at almost any anatomic site, their site of origin is often linked to disease biology. For example, tumors of the ileum typically have a high malignant potential, although metastatic lesions tend to have an indolent course. Gastric and rectal tumors have a low metastatic potential but can grow aggressively once metastatic (1). Gastroenteropancreatic, pulmonary, and thymic NENs are among the most commonly diagnosed (2). The term NENs encompasses both well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas. Whereas neuroendocrine carcinomas are of high grade by default, NETs are classified further according to histologic grade and degree of differentiation, with site-specific parameters (cutoffs). Grading for gastroenteropancreatic NETs, for example, is based on proliferation using either the Ki-67 index or mitotic count per 10 high-power fields. Grade 1 (G1 or low-grade) refers to a Ki-67 of less than 3% and fewer than 2 mitoses per 10 high-power fields, G2 refers to a Ki-67 of 3%–20% or 2–20 mitoses per 10 high-power fields, and G3 refers to a Ki-67 of more than 20% or more than 20 mitoses per 10 high-power fields (3). On the basis of the degree of differentiation, they are categorized as either well-differentiated or poorly differentiated tumors. Most NENs are sporadic, although some arise in the setting of inherited syndromes such as multiple endocrine neoplasia, tuberous sclerosis, Von Hippel–Lindau disease, or neurofibromatosis (1).

NENs typically have increased expression of somatostatin receptors (SSTRs), which are G-protein–coupled receptors modulating cellular proliferative and secretory activity. This expression forms the basis of functional imaging with SSTR-targeting radiopharmaceuticals and treatment with somatostatin analogs (SSAs), including octreotide and octreotate. There are 5 subtypes of SSTRs, with subtypes 2, 3, and 5 most commonly expressed (4). 111In-diethylaminoethyl pentetetradecapeptide–conjugated octreotide (111In-pentetreotide/OctreoScan; Mallinckrodt Nuclear Medicine) was the first agent to receive U.S. Food and Drugs Administration approval (in 1994) for functional imaging of NENs with planar scintigraphy or SPECT (5). 99mTc-labeled SSAs, including the commercially available 99mTc-ethylendiaminediacetic acid hydrazinononicotinamide–[D-Phe1, Tyr2-octreotide], were also developed to improve image quality with lower absorbed radiation dose (6). Newer 67Ga- or 64Cu-tetrateraxetan (DOTA)–conjugated SSAs for PET have shown diagnostic performance superior to that of 111In-pentetreotide and are the current modality of choice for functional imaging (5,7). Different DOTA peptides exist and have varying affinity for the SSTR subtypes (Table 1).

Management of NENs is based on the grade, subtype, distribution, and extent of disease. Anatomic imaging with CT and MRI is standard practice to assess disease location and extent, although...
radiopharmaceutical development has led to improvements in imaging and therapy (together termed theranostics). Initially, high-dose $^{111}$In-pentetreotide was used for therapy (8), via Auger electrons, although the efficacy was limited (9). The use of $^{177}$Lu or $^{90}$Y ($\beta$-emitters) conjugated to SSAs with DOTA has been more effective (10). Specifically, $^{177}$Lu-DOTATATE–based peptide receptor radionuclide therapy (PRRT), studied in a phase 3, multicenter, randomized controlled trial (NETTER-1) in patients with inoperable or advanced and progressive midgut NENs, showed superior outcomes to standard-of-care therapy (10).

This paper reviews the current status and advances in imaging of NENs, with a focus on the use of SSTR PET with respect to PRRT.

### THE ROLE OF CONVENTIONAL IMAGING

CT is commonly the initial imaging modality for evaluation of a suspected NEN. The detection rate of primary small-bowel NENs is about 50% (11,12). Metastatic mesenteric nodes are typically larger than the primary itself and are often calcified. When a small-bowel NEN is known or suspected, a negative oral contrast medium (methylcellulose, polyethylene glycol, or water) is preferred over a conventional radiopaque contrast medium, to avoid masking the primary enhancing lesion on the bowel wall (13,14).

Primary pancreatic NENs have a detection rate of about 80%–100% on CT (15). It is important to obtain an abdominal multiphase CT scan with intravenous contrast medium, since most pancreatic NENs and their hepatic metastases are arterially enhancing and occult on a single portal venous phase (Fig. 1) (11,14,16). Around 22% of pancreatic NENs are arterially hypoenhancing, and in these cases the portal venous and delayed phases can help in detection (11,17).

### NOTEWORTHY

- SSTR PET can be used to reliably assess SSTR expression both visually and semiquantitatively.
- SSTR PET is essential for the proper assessment of eligibility for PRRT.
- SSTR expression is both a prognostic (correlates with outcome regardless of the therapy) and predictive (correlates specifically with response to PRRT) parameter for NENs.

### TABLE 1

<table>
<thead>
<tr>
<th>Radiopeptide</th>
<th>SSTR-2</th>
<th>SSTR-3</th>
<th>SSTR-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{111}$In-DOTANOC</td>
<td>2.9</td>
<td>8</td>
<td>11.2</td>
</tr>
<tr>
<td>$^{111}$In-DOTATATE</td>
<td>1.5</td>
<td>&gt;1,000</td>
<td>547</td>
</tr>
<tr>
<td>$^{111}$In-DOTATOC</td>
<td>4.6</td>
<td>120</td>
<td>130</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTANOC</td>
<td>1.9</td>
<td>40</td>
<td>7.2</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTATATE</td>
<td>0.2</td>
<td>&gt;1,000</td>
<td>377</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTATOC</td>
<td>2.5</td>
<td>613</td>
<td>73</td>
</tr>
</tbody>
</table>

Data are half-maximal inhibitory concentration in nanomoles (lower values represent higher affinity).

MRI is superior to CT for detecting hepatic metastases (18,19). As with CT, multiphase MRI with intravenous contrast medium is recommended since most primary and metastatic NENs show arterial enhancement. Additionally, diffusion-weighted imaging and the delayed postcontrast phase using gadoxetic acid (hepato-specific paramagnetic contrast agent) are useful for detection of hepatic metastases.
metastases. Hepatic metastases typically show a high signal on diffusion-weighted imaging (combination of T2 shine-through and true diffusion restriction), making them more conspicuous; this tool is especially helpful in patients with severe renal failure, for whom intravenous gadolinium is contraindicated (19,20). The most sensitive tool for detection of hepatic metastases is the 20-min postcontrast delayed phase after intravenous administration of gadoxetic acid (Fig. 2), which is retained in hepatocytes but not in metastases, creating a high lesion-to-background contrast on the delayed image. In addition to having high sensitivity for lesion detection, the 20-min delayed phase allows for more accurate and reproducible measurement of baseline and follow-up lesion dimensions on imaging (20–23).

Findings on anatomic imaging associated with higher-grade tumors, which apply to both CT and MRI, include large tumor size (≥2 cm), ill-defined margins, low or moderate arterial hyperenhancement, dilatation of the main pancreatic duct, vascular invasion, and presence of nodal or distant metastases; findings specific to MRI include nonintense T2 signal and, most importantly, high diffusion restriction (24,25). Several studies show that apparent diffusion coefficients inversely correlate with mitotic count and Ki-67 index. A significant difference in apparent diffusion coefficients has been observed between G1 and G2 tumors and between G1/G2 and G3 tumors, with suggested apparent diffusion coefficient cutoffs of below 0.95 × 10⁻³ to 1.19 × 10⁻³ mm²/s for G3 tumors (18,19).

PET RADIOPHARMACEUTICALS

Introduced in 2001, ⁶⁸Ga-DOTATOC was the first PET-SSA ligand (26). As opposed to the SSTR-2–selective DOTATATE, DOTATOC retains an octreotide-like affinity profile (Table 1). (27). A comparison of ⁶⁸Ga-DOTATOC to ⁶⁸Ga-DOTATATE PET/CT in the same patients showed a similar diagnostic accuracy, despite potential advantages for ⁶⁸Ga-DOTATOC in the total number of detected lesions and a higher SUVmax (28). Today, ⁶⁸Ga-DOTATOC and ⁶⁸Ga-DOTATATE are the most commonly used radiopharmaceuticals for imaging NENs, with no clear superiority of either one of these compounds.

One of the main disadvantages of ⁶⁸Ga-SSA–based imaging is the high liver background and short radiopharmaceutical half-life. For the latter, newer SSTR radiopharmaceuticals, such as ⁶⁴Cu-labeled SSA (Food and Drug Administration–approved in September 2020) may provide an advantage. Figure 3 shows the same patient imaged with the 2 different radioisotopes. Potential advantages of ⁶⁴Cu include its longer half-life (12.7 h vs. 68 min for ⁶⁸Ga) and resultant higher target-to-background ratios on delayed imaging, as well as a shorter positron range in tissue (mean, 0.6 mm, vs. 3.5 mm for ⁶⁸Ga). These factors may result in better imaging characteristics, especially at later times (3–24 h after injection) (29). Conversely, ⁶⁴Cu has a significantly lower positron branching ratio (0.17) than ⁶⁸Ga (0.89), which may degrade image quality or at least require a longer acquisition time. A prospective head-to-head comparison of ⁶⁴Cu-DOTATE and ⁶⁸Ga-DOTATOC PET/CT in 59 subjects with NENs showed ⁶⁴Cu-DOTATE to be advantageous, detecting 83% of the true-positive lesions that were discordant between the radiopharmaceuticals (30). However, dual-time-point imaging with ⁶⁴Cu-DOTATE in 35 patients showed similar accuracy for 1-h and 3-h imaging (31), suggesting that the improved detection rate seen in the previous study was due to factors other than the target-to-background ratio. Notably, ⁶⁴Cu-DOTA is prone to demetallation and transchelation in vivo, and better results may be expected with new sarcophagine-based chelators (32).

The SSAs discussed thus far are SSTR agonists, resulting in activation and internalization of the receptor on binding. Radiolabeled SSTR antagonists, such as ⁶⁸Ga-DOTA-JR11, are characterized by a lack of internalization, rapid blood-pool clearance, and greater tumor uptake, aiding detection of metastases (33). A prospective head-to-head comparison between ⁶⁸Ga-NODAGA-JR11, a SSTR antagonist, and ⁶⁸Ga-DOTATOC PET/CT in 12 patients with NENs demonstrated that the favorable biodistribution of the antagonist resulted in a higher detection rate of hepatic metastases and a significantly greater lesion-based overall sensitivity (94% vs. 59%) (34).

When SSTR imaging is suboptimal, other PET agents have been developed to target different receptors overexpressed by the NENs, including the glucagon-like peptide 1 receptor ligand ⁶⁸Ga-DOTA-exendin-4, which may facilitate the detection of benign insulinomas (frequently SSTR-negative) (35,36). The CXCR-4 ligand ⁶⁸Ga-pentixafor seems superior to conventional SSTR imaging for G3 NETs, but its role relative to ¹⁸F-FDG PET remains to be determined (37). SSTR PET typically shows high uptake in well-differentiated or low-grade lesions and lower uptake in poorly differentiated or high-grade lesions. In the latter scenario, ¹⁸F-FDG PET is complementary in that it detects aggressive, poorly differentiated disease with higher grade and worse prognosis (Fig. 4; Supplemental Figs. 1 and 2; supplemental materials are available at http://jnm.snmjournals.org). No more than around 40% of patients with G1 disease are thought to have ¹⁸F-FDG uptake, whereas almost all patients with G3 disease have ¹⁸F-FDG uptake (38–41). Since NENs are vastly heterogeneous and it would be impossible to sample all lesions in

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**FIGURE 3.** ⁶⁸Ga-DOTATATE (A) and ⁶⁴Cu-DOTATATE (B) maximum-intensity-projection PET images of metastatic NEN showing similar findings. Both studies were performed as part of PET/MRI, with uptake times for ⁶⁸Ga-DOTATATE and ⁶⁴Cu-DOTATATE being 113 and 118 min, respectively (3 min/bed position for both).
the body, the combination of SSTR and $^{18}$F-FDG PET provides a noninvasive understanding of disease heterogeneity and likelihood of PRRT response (42).

Currently, $^{18}$F-FDG PET is used for staging G3 disease and can be used to complement SSTR PET when Ki-67 is 10% or more (41). Also, a positive $^{18}$F-FDG PET result may be used to reconsider PRRT for a patient. Specifically, the combination of high SSTR and low $^{18}$F-FDG avidity increases the likelihood of benefit from PRRT; however, the ratio of differentiated to dedifferentiated disease at which PRRT ceases to be useful remains to be determined. In fact, it seems possible that in the event of marked uptake on $^{18}$F-FDG PET, possible because of SSTR-5 binding or tumor heterogeneity. Campana et al. (47) suggested that the SUV$_{max}$ correlated with clinicopathologic features of NENs and could serve as a prognostic index, alongside anatomic location, primary tumor grade, and Ki-67 status. Velikyan et al. (48) reported that kinetic modeling parameters, rather than SUV, reflected receptor density more accurately based on absence of a linear correlation between SUV and net uptake rate in tumors with high SSTR expression. Specifically, SUV$_{v}$s correlated with receptor density at low values, with a nonlinear relationship thereafter leading to underestimation of receptor expression. Although this finding might reflect plasma peptide availability as a limiting factor for tracer uptake in patients with high SSTR expression and high tumor burden, an alternative explanation could be related to receptor saturation.

More recently, volumetric parameters have been evaluated in well-differentiated NENs (49). Specifically, the concept of SSTR-expressing tumor volume, representing the volume of tumor with more than 50% SUV$_{max}$ and total-lesion SSTR expression, calculated as SSTR-expressing tumor volume $\times$ SUV$_{mean}$ in the volume of interest, have been defined. A sum of each of these volumetric parameters can be calculated; the literature suggests there may be a significant correlation between whole-body cumulative SSTR-expressing tumor volume and progression-free survival after PRRT. Nevertheless, estimation of tumor volume based on uptake will likely remain problematic given the intrinsic heterogeneity in tumoral SSTR expression.

Recent guidelines formulated under the auspices of the European Association of Nuclear Medicine recommend the use of $^{68}$Ga-labeled SSAs in combination with CT or MRI for diagnosis, for staging, for restaging after surgery, for following progression, and for known or suspected NETs (50). The National Comprehensive Cancer Network guidelines recommend SSTR PET before PRRT for advanced NENs (51). Although a few studies using $^{68}$Ga-DOTATOC have suggested that SUV$_{max}$ thresholds be used to determine eligibility for PRRT—for example, SUV$_{max}$ cutoffs of 17.9 (52) and 16.5 (53)—differences between scanners and imaging techniques may produce slight variations, which make SUV$_{max}$ problematic to use. An alternative is to use a tumor-to-liver ratio of 2.2 (53). The American College of Radiology practice parameters suggest visually assessed tumor uptake equal to or more than liver uptake as an eligibility criterion for PRRT (54).

The Krenning score was developed using $^{111}$In-pentetreotide scintigraphy (8) and has been extrapolated to SSTR PET (modified Krenning score). A 5-point scale has been proposed on the basis of a qualitative assessment of lesion uptake relative to blood pool and hepatic activity, where 0 is no uptake, 1 is very low uptake, 2 is uptake no more than in the liver, 3 is uptake greater than in the liver, and 4 is uptake greater than in the spleen (55). However, the relationship between the Krenning score from $^{111}$In-pentetreotide scintigraphy and the modified Krenning score from SSTR PET is limited (56). Disease has a bias toward higher scores on SSTR PET than on $^{111}$In-pentetreotide scintigraphy (Supplemental Fig. 3). Part of this bias is due to differences in equipment (higher sensitivity of PET vs. planar scintigraphy or SPECT) and imaging time points ($^{111}$In-pentetreotide scintigraphy at 24 h after injection vs. SSTR PET at 1 h after injection).

Although there are few formal data to support the use of SSTR PET over $^{111}$In-pentetreotide scintigraphy, SSTR PET has become the standard for pre-PRRT patient selection because of its higher sensitivity, faster imaging times, and lower radiation dose. For lesions larger than 2 cm, it is appropriate to use the modified Krenning score, and PRRT should be considered with a score of 3 or 4. Caution should be used before treating patients with lesions smaller than 2 cm with a modified Krenning score of 3 or 4, as these patients are unlikely to have fulfilled criteria if imaged with $^{111}$In-pentetreotide. This is to emphasize that the current data do not provide

![FIGURE 4. Maximum-intensity projection images of patient with metastatic grade 1 (Ki-67 < 2%) NEN from small-bowel primary. (A) $^{68}$Ga-DOTATATE PET shows prominent uptake in primary tumor, lymphadenopathy, and liver metastases. (B) $^{18}$F-FDG PET shows no abnormal uptake (arrow points out incidentally noted fractured rib).](image-url)
sufficient evidence for the use of SSTR PET in this setting. PRRT should not be considered when lesions show no or low uptake on SSTR PET.

**REPORTING SSTR PET**

There is a need for standardized interpretation of SSTR PET given that findings on baseline imaging partly determine treatment success with radioligand therapies (57). The report (Supplemental Fig. 4) should include a concise clinical history, including NEN subtype, tumor grade and differentiation, and prior treatments (medical or surgical). The imaging parameters, in terms of the specific radiopeptide and its administered activity, uptake time, duration of imaging (time per bed position), and area imaged, should be documented. Comparison and correlation with any prior SSTR imaging, 18F-FDG PET, and other anatomic imaging should be performed. Findings should detail the site and size of the lesions (the latter if seen on corresponding CT/MRI) and uptake intensity, which can be expressed semiquantitatively (commonly as SUVmax). The pattern of uptake can help in the differentiation between benign and malignant lesions.

The NETPET score is a grading system that combines findings on SSTR and 18F-FDG PET with a single parameter (58). This scoring system has been developed as a prognostic biomarker. Although rarely included in reports since SSTR and 18F-FDG PET are not routinely performed together, its rate of inclusion may change in the future.

The SSTR reporting and data systems (RADS) has also been introduced as part of the umbrella molecular imaging RADS, a 5-point scale (from 1 [no evidence of disease and definitely benign] to 5 [high certainty of NEN]) indicating both disease site and radiotracer avidity (35). SSTR RADS entails a 3-point qualitative scoring of uptake level, where up to 5 target (largest, most avid) lesions can be identified, with overall score defined as the highest scored lesion. A summed RADS score, including all 5 target lesions, has also been suggested (59). Future validation of this framework is warranted, including inter- and intraobserver agreement studies and histopathology correlation.

**Disease Burden, Outcome Prediction, and Response Assessment**

SSTR expression is both a prognostic (correlates with outcome regardless of therapy) and predictive (correlates specifically with response to PRRT) parameter for NENs. (60). The current literature suggests that higher baseline SUVs on SSTR PET predict better response to PRRT outcomes. Oksuz et al. (52) reported that high pretherapy primary tumor uptake suggested a good response to PRRT; Kratochwil et al. (53) reported that high pretherapy uptake in liver metastases suggested a good response; and Ambrosini et al. (60) reported better outcomes in patients with high baseline SUVs. To avoid scanner-related variations, parameters such as tumor-to-liver and tumor-to-spleen ratios may be used. It has been reported that a tumor-to-liver ratio of more than 2.2 is predictive of a favorable response. It has, however, been demonstrated that a high uptake (e.g., Krenning grade 4) is associated with response to PRRT in only 60% of patients (61).

The literature on response evaluation is more variable, and we are only beginning to understand how post-therapy SSTR PET correlates with endpoints such as time to progression, progression-free, and overall survival. Haug et al. (62) studied SUVmax and tumor-to-spleen ratio for prediction of time to progression and clinical outcome after a first PRRT cycle in well-differentiated NENs. The authors found that reduced uptake after therapy predicted time to progression and correlated with clinical improvement. Further, interval change in tumor-to-spleen ratio was superior to interval change in SUVmax. Meanwhile, Gabriel et al. (6) reported essentially random SUV fluctuations after PRRT. The question remains: Does diminishing tumor radiotracer uptake reflect true disease improvement or is there a higher degree of tumor dedifferentiation with loss of SSTR expression? Accordingly, the recently updated appropriate use criteria (63) for SSTR PET notes that response should be assessed by the disappearance of known lesions or development of new lesions, rather than changes in SUVs.

Monitoring response to PRRT with SSTR PET and attempting to interpret the biologic significance of tumor uptake change are challenging. One study evaluated 46 patients with advanced NENs treated with 2–7 cycles of PRRT and compared the results from the post-therapy 68Ga-DOTATATE PET to CT/MRI with RECIST. The authors found little advantage to SSTR PET over conventional imaging for response assessment (6). In another study, of 66 patients, 68Ga-DOTATOC and 18F-FDG PET was done at baseline, at 3 mo, and again at 6–9 mo after completion of PRRT. The authors concluded that uptake on 18F-FDG PET at baseline and follow-up had a stronger correlation with the outcome than did SSTR PET and that combination imaging with both radiopharmaceuticals might be advisable across all tumor grades (43).

Also, a high overall tumor burden and tumor heterogeneity on SSTR PET is likely to be associated with worse prognosis. SSTR PET helps in assessing the heterogeneity of NENs that exist at the interpatient, intrapatient, interlesional level at a specific time point or longitudinally at different time points. This heterogeneity implies a variety of cells displaying variable characteristics in terms of metabolism, proliferation, metastatic potential, and therapy response. Distinct metastases may harbor different cellular clones with varying SSTR expression. The primary tumor and its metastases may also differ. Indeed, this may impact the chance of PRRT success and explains why cure is rarely possible with systemic metastatic disease. In a study by Graf et al. (64), only patients with at least 90% of metastases positive for SSTR were treated with PRRT. Positive lesions were viewed in 3 dimensions.
and a lesion that had a change in score from 3 or 4 to 2, or from 2 to 1, that persisted over more than 5 mm in any plane was defined as heterogeneous. Only the solid portion of a necrotic lesion was assessed. If more than 50% of lesions were deemed heterogeneous, the patient was labeled as heterogeneous. This study confirmed that heterogeneity had a negative impact on overall survival and time to progression after PRRT. Indeed, heterogeneity surpassed Ki-67 as a prognostic marker, especially related to PRRT, reinforcing the suspicion that PRRT may target the less aggressive, SSTR-positive cells, sparing the rest. Thus, even when decreased tumor size suggests response by RECIST, the more aggressive cells might remain viable. These observations highlight an intrinsic flaw of using quantitative parameters such as SUVmax alone, which do not account for the intralesional variation in SSTR expression. Interestingly, some authors have observed that, after PRRT, heterogeneous lesions may become more homogeneous. In the future, use of textural characteristics such as entropy and skewness may prove superior to our current methodology for lesion analysis.

Recently, a prospective study on 158 patients divided into 3 independent 
\[131^]\text{I}-\text{Lu}-\text{PRRT} cohorts demonstrated that specific circulating tumor transcripts (messenger RNA) specifically predict the outcome of PRRT and therefore represent a marker of radiosensitivity (65), whereas the circulating transcript signature NETest allows accurate monitoring of the course of disease during treatment and integrates with imaging (66).

The primary site of the tumor, which can often be elucidated with SSTR PET, is a prognostic factor and should be incorporated in the decision algorithm for PRRT. Midgut and pancreatic NENs are included in the Food and Drug Administration-approved indications for PRRT. Bronchial NENs represent a special category, with typical tumors considered more appropriate for PRRT because of higher SSTR expression. In the case of a pheochromocytoma or paraganglioma, the current recommendation reserves PRRT for metastoidobenzylguanidine-negative tumors only, for which \[131^]\text{I}-\text{metaiodobenzylguanidine} treatment is precluded. The distribution and extent of disease, ideally evaluated with SSTR PET, also affects management. In general, caution is needed in tumors with extensive mesenteric and peritoneal involvement, since PRRT may increase the risk of complications from a desmoplastic reaction. As the tumors metastasize, the total tumor burden may play a role, depending on the primary site of disease. For example, pancreatic NENs with more than 25% liver involvement and bone metastases have worse prognosis, whereas gastric NENs show no significant difference in outcome based on distribution (67). In general, tumor burden is termed limited if fewer than 5 lesions are detected at 1 site, moderate if more than 5 lesions at 2 sites, and extensive if more than 2 sites are involved, and this affects the treatment approach (Fig. 5). Most gastroenteropancreatic NENs present with hepatic metastases at diagnosis despite low Ki-67, and the presence of hepatic metastases profoundly decreases overall survival. PRRT may be helpful for nonresectable hepatic metastases and indeed may render the lesions resectable. In liver-dominant disease, intraarterial PRRT is being investigated.

CONCLUSION

SSTR PET is the preferred imaging modality at initial diagnosis of low- and intermediate-grade NENs, especially for localization of the primary tumor and determining disease extent. SSTR PET is essential for selecting patients for PRRT, whereas its role in response monitoring is still being evaluated. Although SSTR expression can be assessed visually and semiquantitatively, with various suggested thresholds, a modified Krenning score is used in current clinical practice.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES


