Theragnostics in Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine tumor • Theragnostics • ^{68}Ga-DOTA-TOC • ^{18}F-FDG
• Peptide receptor radionuclide therapy • ^{177}Lu-PRRT • ^{90}Y-DOTATATE

KEY POINTS

- Somatostatin receptor (SSTR)-imaging (PET or conventional scintigraphy) is an effective tool for diagnosis, staging, planning of peptide receptor radionuclide therapy (PRRT), and evaluation of treatment response in patients with neuroendocrine tumors (NETs).
- Applying a dual-tracer approach with SSTR and PET with fludeoxyglucose F 18 imaging can help the decision-making process for therapy selection in patients with NET.
- PRRT appears to be the most effective therapeutic option in the management of patients with inoperable or metastasized NET with limited side effects if dose limits are respected.

INTRODUCTION

Neuroendocrine tumors (NET) constitute a heterogeneous group of tumors that are able to express somatostatin receptors (SSTRs) on the cell surface,[1,2] allowing the use of radiolabeled somatostatin analogs for SSTR-targeted imaging as well as peptide receptor radionuclide therapy (PRRT).

NETs are considered a relatively rare disease, although incidence rates have been rising over the past 30 years in Europe and the United States,[1,2] particularly those arising from the midgut and pancreas.[3] Located primarily with approximate 72% in the gastrointestinal tract and 25% in the bronchopulmonary system, NETs can also originate from various other sites such as the head and neck region or the prostate.[4,5] They can be asymptomatic for years and, especially those of the pancreas and intestine, they are often diagnosed at late stage when metastatic or locally advanced[6,7] and therefore inoperable, so that a systemic therapy is often required.[4,8]

The clinical course of NET can be quite heterogeneous with variable response to treatments despite possessing similar tumor characteristics and having received the same therapy. The World Health Organization (WHO) guidelines classify NET into 3 grades based on cell proliferation, the number of mitoses, and the expression of the nuclear antigen Ki-67.[4] Both proliferation index and grade strongly correlate with tumor behavior and prognosis.[9–11] High-grade, poorly differentiated NETs often have limited expression of SSTR,[9] what can lead to false negative SSTR-imaging results and makes the molecular investigation difficult.

For the choice of the most appropriate treatment for NET, information regarding anatomic location and local invasion of adjacent structures, tumor functionality, histologic tumor grading, staging, and SSTR status are required to help the decision-making process, which should be individualized for patients with NET.

CLINICAL CARE POINTS

The theragnostic principle is based on the concept of diagnostic molecular imaging, followed by an individually tailored treatment decision. Several studies have demonstrated the effectiveness of the application of SSTR-targeted imaging (PET or conventional scintigraphy) for diagnosis, staging, and planning of PRRT, as well as evaluation of response to the treatment.[4,6,7,12]

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Imaging in Neuroendocrine Tumors

Assessment of liver metastases and degree of liver involvement using morphologically orientated imaging techniques, such as ultrasonography, contrast-enhanced multidetector computed tomography (CT), or MR imaging is central for accurate staging and for evaluating the response to treatment.[13] However, these methods sometimes lack specificity, as conclusions regarding malignant involvement of organ structures are based only on size criteria and the contrast enhancement pattern.[14]

SSTR expression is evaluated by SSTR-imaging with Gallium 68 (^{68}Ga)–1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)- Phe^{1}-Tyr^{3}-Octreotide (TOC)/ Tyr^{3}-Octreotate (TATE)/ Nal^{3}-Octreotide (NOC)/lanreotide PET/CT or ^{99m}Tc-hydrazinonicotinyl (HYNIC)-TOC/^{111}In-DOTA-TOC/lanreotide scintigraphy,[4,14–17] among others. The whole-body nature of the examination as well as its noninvasiveness makes SSTR-imaging (PET or scintigraphy) more appealing for imaging of NET than morphologic techniques.

Gabriel and colleagues[16] found that ^{68}Ga-DOTA-TOC PET shows a significantly higher detection rate compared with conventional SSTR scintigraphy and diagnostic CT with clinical impact in many patients. Furthermore, in terms of staging SSTR PET/CT imaging has been shown to be superior to CT and MR imaging as well.[14,17,18]

PET/computed tomography imaging with Gallium 68–labeled somatostatin analogs

The Ga-complexes of somatostatin analogs commonly show a higher binding affinity for sstr2 when compared with the corresponding complexes with indium, yttrium, or lutetium. DOTA-lanreotide when labeled with yttrium beside high affinity to sstr2 also shows high affinity to sstr5 comparable with DOTA-NOC and low affinity to sstr3 (for review see Ref.[19]).

The increased hydrophilicity of the Ga-complex results in an increased renal elimination. Together with an improved accumulation of ^{68}Ga-DOTA-TOC in the tumor lesions, these pharmacokinetic properties lead to a high lesion contrast within a short time interval post injection, which is of particular importance considering the short half-life of ^{68}Ga (68 minutes).[19] A detailed procedure guideline for PET-CT with ^{68}Ga-labeled somatostatin analogs peptide imaging was summarized by the Oncology Committee of the European Association of Nuclear Medicine.[20]

In the past few years, PET/CT imaging with ^{68}Ga-labeled somatostatin analogs (^{68}Ga-DOTA-TOC/TATE/NOC or ^{68}Ga-DOTA-lanreotide) has been shown to provide excellent sensitivity and specificity for diagnosing and staging NET.[16,21]

However, the very specific binding of these compounds may lead to overinterpretation of tracer accumulation. Therefore, interpretation must be done cautiously in organs showing physiologically enhanced tracer uptake, including exocrine pancreas (head/uncinate process),[22] spleen, liver, pituitary, thyroid, kidneys, adrenal glands, and salivary glands.[22] Infection/inflammation can lead to false positive results.[23]

Gabriel and colleagues[16] showed that ^{68}Ga-DOTA-TOC provided additional information that was obtained with none of the other imaging procedures in 25% (21/84) of patients with NET. Haug and colleagues[24] demonstrated the utility of ^{68}Ga-DOTA-TATE PET/CT in 104 patients with suspected NET. PET/CT showed a sensitivity of 81% and a specificity of 90% resulting in an accuracy of 87%. The Munich Group[25] also reported change in surgical management in 9 (20%) of 44 patients with NET. In a retrospective blinded review, Hofman and colleagues[26] communicated high impact on patient management including curative surgery by identifying a primary site and directing patients with multiple metastases to systemic therapy.

Our Innsbruck Group[27] reported that ^{68}Ga-DOTA-TOC showed in patients with NET a significantly higher maximum standard uptake value (SUVmax) regarding the primary tumor (n = 25) as well as liver metastases (n = 30) compared with ^{68}Ga-DOTA-LAN. Furthermore, we found that investigation only of SSTR status by ^{68}Ga-DOTA-TOC PET/CT may not reflect progression in a certain NET lesion.[28] Moreover, high-grade, poorly differentiated NET often has limited expression of SSTR,[10] what can lead to false negative SSTR-imaging results and makes the molecular investigation difficult. Therefore, applying a dual-tracer approach with SSTR and PET with fludeoxyglucose F 18 (^{18}F-FDG-PET) imaging could help the decision-making process for therapy selection in patients with NET.

PET/computed tomography imaging with fludeoxyglucose F 18

^{18}F-FDG-PET is used to assess glycolytic metabolism, and higher uptake of ^{18}F-FDG has been linked with more aggressive tumor features.[29] ^{18}F-FDG-PET is widely applied in oncology, but its use in NET has been a matter of controversy.[28]

The higher the grade of an NET, the higher is the prevalence of glucose hypermetabolic tumors.[30] A dichotomous behavior has been found between SSTR imaging and ^{18}F-FDG-PET in well-differentiated and poorly differentiated NET, where

the former was more positive with SSTR imaging[30,31] and the latter with ^{18}F-FDG-PET.[32,33] ^{18}F-FDG PET/CT has thus been used increasingly in the past few years for the evaluation of high-grade NET.[29,30] The diagnostic value of ^{18}F-FDG PET in lower grade NET is limited because they are slowly proliferating tumors with lower glycolytic activity.[34] Hence, even though ^{18}F-FDG-PET has a high spatial resolution, it has not been indicated primarily for NET.

Binderup and colleagues[35] showed that although the diagnostic sensitivity of ^{18}F-FDG PET is low for NET, the prognostic value is high. This makes the low diagnostic sensitivity less important because a negative ^{18}F-FDG-PET result is predictive of low aggressiveness and a high survival rate.

Garin and colleagues[36] reported that ^{18}F-FDG-PET has a prognostic value for early tumor progression. Our Group[28] also showed that the presence of ^{18}F-FDG-positive tumors correlates strongly with a higher risk of progression. We found that initially ^{18}F-FDG-negative patients with NET may show ^{18}F-FDG-positive tumors during follow-up. Furthermore, we observed that patients with well-differentiated, G1 and G2 NET also may have ^{18}F-FDG-positive tumors initially and may develop ^{18}F-FDG-positive lesions during follow-up.

Some studies have demonstrated the association of ^{18}F-FDG PET with treatment response and progression-free survival after PRRT in NET. Zhang and colleagues[37] reported a significant benefit in overall survival and in progression-free survival for their ^{18}F-FDG-negative group. These investigators found that the presence of positive lesions on ^{18}F-FDG PET is an independent prognostic factor in patients with NET treated with PRRT. High SSTR expression combined with negative ^{18}F-FDG PET/CT imaging is associated with the most favorable long-term prognosis. However, the prognostic value of ^{68}Ga-SSTR PET imaging was found to be lower than that of the ^{18}F-FDG PET.

High ^{18}F-FDG SUV seems to strongly correlate with a short survival in patients with NET. Binderup and colleagues[35] reported that a SUVmax higher than 3 was found to be the only independent predictor of progression-free survival and that an ^{18}F-FDG SUVmax higher than 9 was strongly correlated with a greater risk of mortality in patients with NET.

Metabolic imaging with ^{18}F-FDG PET/CT complements thus the molecular imaging with ^{68}Ga-SSTR PET/CT for the prognosis of survival after PRRT.[35,37]

Peptide Receptor Radionuclide Therapy

For the choice of the most appropriate treatment for NET, information regarding anatomic location and local invasion of adjacent structures, tumor functionality, histologic tumor grading, staging, and SSTR status are required to help the decision-making process, which should be individualized for patients with NET.

Multiple treatment approaches, which are interchangeable for most patients, are now available for patients with NET presenting with metastatic disease, including surgery, locoregional therapies,[4,8,9] interferon-alpha, chemotherapy,[8,9] molecular targeted therapies,[10,38] biotherapy with somatostatin analogs,[38–40] and PRRT[4,15,21,40]; however, relapses occur after a certain time in many patients.

PRRT is a molecularly targeted radiation therapy involving the administration of a specific radiopharmaceutical composed of a β-emitting radionuclide chelated to a peptide designed to target with high affinity SSTR overexpressed on tumors. SSTR 2 is the key target molecule for both cold and radiolabeled somatostatin analogs.[4] PRRT using ^{177}Lu and/or ^{90}Y-labeled somatostatin analogs (DOTATATE, DOTATOC, or lanreotide) has been used for more than 20 years as a systemic treatment approach in metastatic and inoperable NET that expresses SSTR positivity, evaluated by SSTR-imaging (PET and/or conventional scintigraphy).[41–43]

Depending on the size of the tumor or metastasis, ^{90}Y beta rays with a range of approximately 12 mm in tissue are theoretically better suited for larger tumor lesions, whereas ^{177}Lu, with a smaller range of approximately 2 mm, is preferentially used for smaller tumors.[41] Although there is no evidence in the clinical setting, this concept has been widely applied in clinical practice for many years. In the past few years, the ^{177}Lu-labeled compound, particularly, has found its way into clinical routine in view of its more favorable properties in terms of kidney toxicity.

There are different research PRRT protocols in use with either standard dose or individualized therapy with a variable number of cycles. In most institutions, PRRT treatment scheme is individually adapted concerning the doses and time intervals, depending on tumor stage, age, tracer uptake, biochemical response, Karnofsky Index, and quality of life. The PRRT scheme that has been performed in Innsbruck for more than a decade includes a PRRT infusion administered in conjunction with an amino acid solution to protect the kidney function.[4,41]

The recommended intravenously administered activity for ^{90}Y-DOTA-TOC/TATE is 2.78 to 4.44 GBq (75–120 mCi) every 6 to 12 weeks for a total of 2 to 4 cycles, and for ^{177}Lu-DOTATATE/TOC is 5.55 to 7.4 GBq (150–200 mCi) every 6 to 12 weeks for a total of 3 to 5 cycles. Restaging with SSTR-imaging, CT, and laboratory analyses, among others, is performed after completion of the

therapy cycles and in many institutions also between cycles. Combination therapies with ^{90}Y and ^{177}Lu peptides are being actively investigated.[4]

The long-acting form (cold, ie, nonradioactive) of the somatostatin analogs octreotide or lanreotide can be applied between the treatment cycles but should be at least 4 weeks apart from the radioactive cycle.[43]

In general, PRRT is used after failing first-line medical therapy. The main candidates for PRRT are those with well-differentiated and moderately differentiated NET defined as NET grade 1 or 2 according to the WHO 2010 classification.[10] Retrospective multicenter ongoing studies, such as on behalf of the World Association of Radiopharmaceutical and Molecular Therapy, are being conducted to evaluate the efficacy of PRRT also in patients with NET grade 3.

The clinical efficacy of PRRT has been demonstrated in several clinical studies[40–42] (**Fig. 1**). The documented response rate summing up complete response, partial response, minor response, and stable disease is approximately 70% to 80% for ^{90}Y-DOTATOC and for ^{177}Lu-DOTATATE.[41,42]

PRRT has been shown also effective in terms of both symptomatic control and survival.[40–42] Recently, in a 12-year follow-up after PRRT performed at our institution, Gabriel and colleagues[41] found that 32% (14 of 44 patients) of the patients with metastatic or inoperable NET disease are still alive more than 12 years after the beginning of PRRT, with a median overall survival of 79 months. Other recent study results have indicated also a benefit of PRRT concerning response rate, progression-free survival, and overall survival as compared with established therapy procedures.[40,44] In particular for metastatic midgut NETs, PRRT has been established as one major therapy strategy because only a few therapeutic alternatives are available for this tumor entity.[45]

The significant benefit of PRRT over cold somatostatin analog therapy was demonstrated by the recent randomized phase 3 clinical trial of ^{177}Lu-DOTATATE in advanced, progressive midgut NETs grade 1 or 2 (NETTER-1).[40] In this trial, PRRT resulted in a markedly longer progression-free survival and a significantly higher response rate compared with long-acting repeatable octreotide alone.

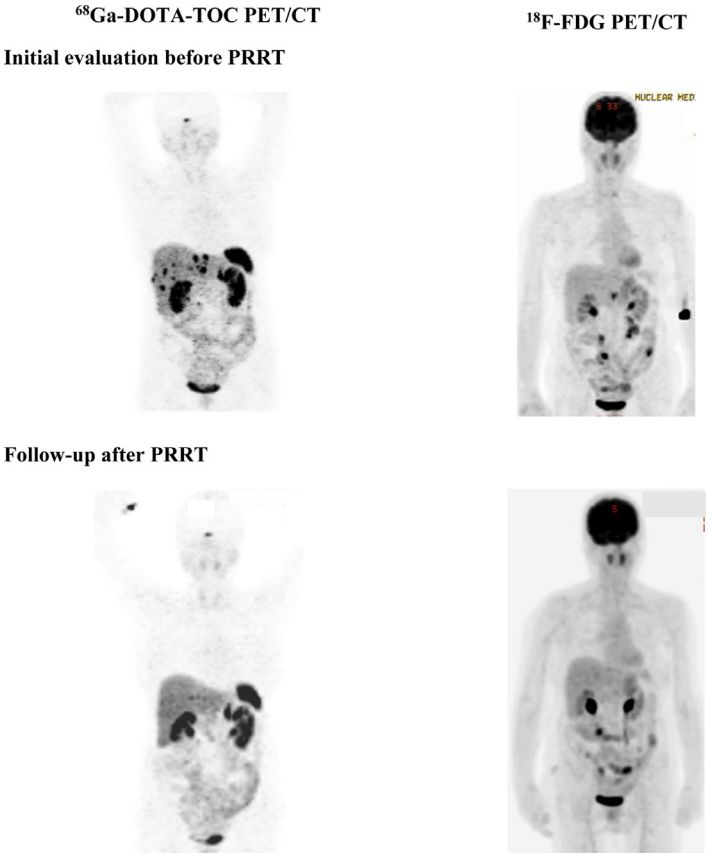

Fig. 1. A 59-year-old female patient with pancreatic NET and liver metastases before PRRT shown by ^{68}Ga-DOTA-TOC PET, whereas ^{18}F-FDG PET was negative (*upper row*). Complete remission documented by ^{68}Ga-DOTA-TOC and ^{18}F-FDG PET (*lower row*) after PRRT (9 cycles with ^{90}Y-DOTA-TOC, cumulative dose of 10 GBq, and 4 cycles with ^{177}Lu-DOTATATE, cumulative dose of 29 GBq).

Forrer and colleagues[46] reported that ^{177}Lu-DOTATOC therapy is feasible, safe, and efficacious in patients with relapse after ^{90}Y-DOTATOC treatment.

Health-related quality of life (HRQoL) is also significantly improved after PRRT.[40,47–49] Our group[50] examined the course of HRQoL in patients with metastatic gastroenteropancreatic NET undergoing PRRT at our institution. We found a significant improved or at least stable HRQoL on several domains from baseline to the first restaging after PRRT regarding physical, social and role functioning, fatigue, diarrhea, and appetite loss.

Several articles have been published on toxicity following PRRT proving that the treatment is safe and beneficial.[40,42,51] Dosimetry is useful to assess the radiation risk for normal and critical organs, that is, bone marrow and kidneys after PRRT. Radiolabeled SST-analogs are reabsorbed in the renal proximal tubules, hence the kidneys are exposed to a relatively high radiation dose. Renal radiation exposure can be reduced by coinfusion of amino acids during PRRT.[52] The standard activity of ^{177}Lu and ^{90}Y-labeled somatostatin analogs may be reduced in the case of pretherapeutic relevant renal impairment, or low white blood cell count.[53]

Severe toxicity (any grade greater than grade 2) according to the Common Terminology Criteria of Adverse Events (CTCAE), occur rarely.[53] Bodei and colleagues[51] reported nephrotoxicity of any CTCAE grade in 34.6% and grade 3 and 4 in 1.5% for a very inhomogeneous cohort of 807 patients studied. In our retrospective analysis[53] the vast majority of patients showed either none or only a mild to moderate decrease in kidney function as well as hematotoxicity 1 year after completion of standardized PRRT with 4 treatment cycles of either ^{90}Y-somatostatin or ^{177}Lu-somatostatin analogs. We found nephrotoxicity of any CTCAE grade in 31 (30.4%) of 102 patients and severe (CTCAE grade 3/4) in only 1 patient. In our cohort, PRRT had no statistically significant impact on leukopenia and thrombopenia. No hematotoxicity greater than grade 2 according to CTCAE was observed.

Therefore, in terms of safety, PRRT seems to have no critical impact on further oncologic treatment options in the case of disease progression.

In case of dedifferentiation, higher grade, bulky or ^{18}F-FDG-avid NET (**Fig. 2**) chemotherapy may become an option. The integration of PRRT into multimodality therapy protocols might improve response to treatment. The use of radiosensitizing

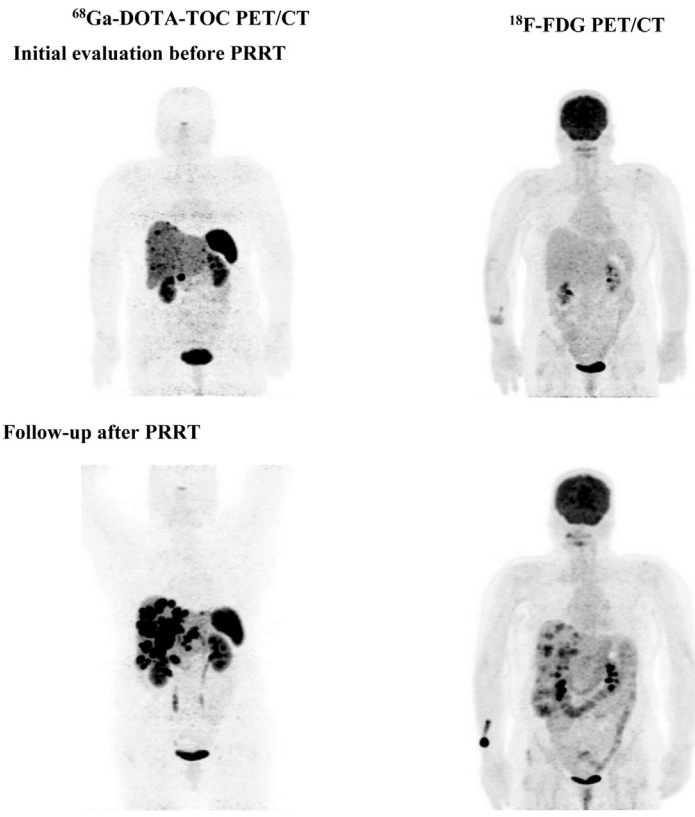

Fig. 2. A 55-year-old female patient with pancreatic NET and liver metastases before PRRT shown by ^{68}Ga-DOTA-TOC PET, whereas ^{18}F-FDG PET was negative (*upper row*). Disease progression documented by ^{68}Ga-DOTA-TOC and ^{18}F-FDG PET (*lower row*) after PRRT (5 cycles with ^{90}Y-DOTA-TOC, cumulative dose of 19.37 GBq). Biopsy of a hypermetabolic liver metastasis revealed a Ki-67 index of 40%.

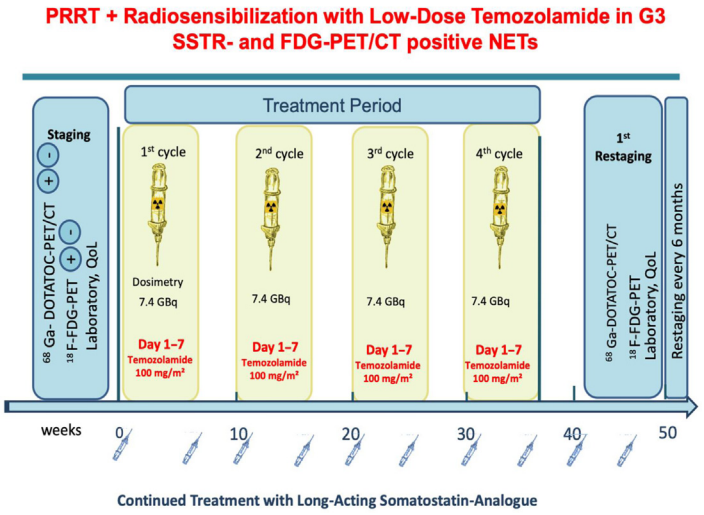

Fig. 3. Innsbruck scheme of PRRT in combination with radiosensibilization with low-dose temozolomide in G3 SSTR- and ^{18}FDG-PET/CT positive NET. QoL, evaluation of health-related quality of life.

chemotherapy in combination with ^{90}Y-somatostatin or ^{177}Lu-somatostatin analogs has shown an additive value.[54]

We investigated recently (data under publication, 2021) the efficacy of PRRT in combination with radiosensitizing chemotherapy with temozolomide (**Fig. 3**) in 20 patients with G3 NET with ^{18}F-FDG-avid lesions. At the end of the observation time, 20% of patients had complete response, 10% patients partial response, 30% patients stable disease, and 40% patients progressive disease. None of our patients showed serious adverse events after this combined treatment during follow-up.

DISCUSSION

Our group[9] showed recently that the sole investigation of SSTR status by ^{68}Ga-DOTA-TOC-PET/CT may not reflect the progression in certain NET lesions. Therefore, we recommended performing ^{18}F-FDG-PET in the initial evaluation and during follow-up of patients with NET, especially when SSTR PET/CT shows progression. ^{18}F-FDG-PET/CT along with SSTR imaging was found to help to stratify patients with G3 NET. High uptake on ^{68}Ga-SSTR PET/CT combined with negative ^{18}F-FDG PET/CT is associated with a comparatively prolonged progression-free as well overall survival.[37] ^{18}F-FDG-PET/CT is thus a complementary tool to ^{68}Ga-DOTA-TOC-PET/CT with clinical relevance for the molecular investigation of NET. These findings must be taken into account, especially for individualized and optimized therapy planning.

PRRT appears to be the most effective therapeutic option in the management of inoperable or metastasized patients with NET.[40–42] However, despite the huge potential of PRRT the nonavailability of PRRT in many countries still limits its widespread use.

The combined use of different radiolabeled somatostatin analogs, sequentially or concomitantly, may optimize the treatment outcome. Over time, several patients with differentiated NET will show progressive disease after initial response to PRRT. In these patients, re-PRRT may be a favorable option.[43]

On the other hand, PRRT also entails limited side effects that should be considered. In particular, special attention has to be paid to renal function and bone marrow reserve.[42,51] Protective measures, particularly individually adapted PRRT concerning the doses and time intervals and also concomitant application of amino acid solution to protect the kidney function should be undertaken regularly.

When NETs lose their initially high differentiation, the European Neuroendocrine Tumor Society Consensus Guidelines propose molecular targeted therapies, and in the case of higher dedifferentiation, they suggest chemotherapy.[10] Further ongoing studies are mandatory to optimize clinical protocols and assess the efficacy of PRRT in combination with radiosensitizing chemotherapy in patients with ^{18}F-FDG-avid NET lesions.

SUMMARY

Adopting a dual-tracer approach encompassing SSTR and ^{18}F-FDG-PET imaging, and assessing the SSTR expression and glycolytic metabolism, respectively, contribute toward a personalized medicine in the management of patients with NET.

PRRT with differently labeled tracers (^{90}Yor ^{177}Lu) and different somatostatin analogs is

generally well tolerated, with only a few serious side effects.

Relapses occur after a certain time in many patients with NET. In these cases, the combined use of different radiolabeled somatostatin analogs, sequentially or concomitantly, as well as re-PRRT may optimize the treatment outcome.

REFERENCES

1. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 2003; 24(4):389–427.
2. Reubi JC, Schär JC, Waser B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 2000;27(3):273–82.
3. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9(1):61–72.
4. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013;40(5):800–16.
5. Quaedvlieg PF, Visser O, Lamers CB, et al. Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. Ann Oncol 2001;12(9):1295–300.
6. Hallet J, Law CH, Cukier M, et al. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer 2015;121:589–97.
7. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.
8. Steinmüller T, Kianmanesh R, Falconi M, et al. Consensus guidelines for the management of patients with liver metastases from digestive (neuro) endocrine tumors: foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2008;87: 47–62.
9. Ramage JK, Goretzki PE, Manfredi R, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors: well-differentiated colon and rectum tumor/carcinoma. Neuroendocrinology 2008;87:31–9.
10. Pavel M, Baudin E, Couvelard A, et al. ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012;95:157–76.
11. Rindi G. The ENETS guidelines: the new TNM classification system. Tumori 2010;96:806–9.
12. Strosberg J, Nasir A, Coppola D, et al. Correlation between grade and prognosis in metastatic gastroenteropancreatic neuroendocrine tumors. Hum Pathol 2009;40:1262–8.
13. Sundin A, Vullierme MP, Kaltsas G, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. Neuroendocrinology 2009;90(2):167–83.
14. Gabriel M, Hausler F, Bale R, et al. Image fusion analysis of ^{99m}Tc-HYNICTyr3-octreotide SPECT and diagnostic CT using an immobilization device with external markers in patients with endocrine tumours. Eur J Nucl Med Mol Imaging 2005;32:1440–51.
15. De Jong M, Breeman WAP, Kwekkeboom DJ, et al. Tumor imaging and therapy using radiolabeled somatostatin analogues. Acc Chem Res 2009;42(7): 873–80.
16. Gabriel M, Decristoforo C, Kendler C, et al. ^{68}Gallium-DOTA-Tyr(3)-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. J Nucl Med 2007;48:508–18.
17. Naswa N, Sharma P, Kumar A, et al. Gallium-68-DOTA-NOC PET/CT of patients with gastroenteropancreatic neuroendocrine tumors: a prospective single-center study. Am J Roentgenol 2011;197: 1221–8.
18. Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with neuroendocrine tumor: ^{68}Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. J Nucl Med 2009;50:1214–21.
19. Virgolini I, Gabriel M, Kroiss A, et al. Current knowledge on the sensitivity of the (68)Ga-somatostatin receptor positron emission tomography and the SUVmax reference range for management of pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2016;43(11):2072–83.
20. Virgolini I, Ambrosini V, Bomanji JB, et al. Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging 2010;37:2004–10.
21. Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of ^{68}Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. J Nucl Med 2016;57:708–14.
22. Castellucci P, Pou Ucha J, Fuccio C, et al. Incidence of increased ^{68}Ga-DOTANOC uptake in the pancreatic head in a large series of extrapancreatic NET patients studied with sequential PET/CT. J Nucl Med 2011;52:886–90.
23. Ambrosini V, Campana D, Tomassetti P, et al. ^{68}Ga-labelled peptides for diagnosis of gastroenteropancreatic NET. Eur J Nucl Med Mol Imaging 2012;39:S52–60.
24. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. The role of ^{68}Ga-DOTATATE PET/CT in suspected

neuroendocrine tumors. J Nucl Med 2012;53:1686–92.
25. Ilhan H, Fendler WP, Cyran CC, et al. Impact of ^{68}Ga-DOTATATE PET/CT on the surgical management of primary neuroendocrine tumors of the pancreas or ileum. Ann Surg Oncol 2015;22:164–71.
26. Hofman MS, Kong G, Neels OC, et al. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. J Med Imaging Radiat Oncol 2012;56:40–7.
27. Putzer D, Kroiss A, Waitz D, et al. Somatostatin receptor PET in neuroendocrine tumours: ^{68}Ga-DOTA0, Tyr3-octreotide versus ^{68}Ga-DOTA0-lanreotide. Eur J Nucl Med Mol Imaging 2013;40:364–72.
28. Nilica B, Waitz D, Stevanovic V, et al. Direct comparison of (68)Ga-DOTA-TOC and (18)F-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle. Eur J Nucl Med Mol Imaging 2016;43(9):1585–92.
29. Kwee TC, Basu S, Saboury B, et al. A new dimension of FDG-PET interpretation: assessment of tumor biology. Eur J Nucl Med Mol Imaging 2011;38(6):1158–70.
30. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using ^{68}Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and ^{18}F-FDG. Cancer 2008;112:2447–55.
31. Sharma P, Naswa N, Kc SS, et al. Comparison of the prognostic values of ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT in patients with well-differentiated neuroendocrine tumor. Eur J Nucl Med Mol Imaging 2014;41:2194–21202.
32. Basu S1, Sirohi B, Shrikhande SV. Dual tracer imaging approach in assessing tumor biology and heterogeneity in neuroendocrine tumors: its correlation with tumor proliferation index and possible multifaceted implications for personalized clinical management decisions, with focus on PRRT. Eur J Nucl Med Mol Imaging 2014;41:1492–6.
33. Belhocine T, Foidart J, Rigo P, et al. Fluorodeoxyglucose positron emission tomography and somatostatin receptor scintigraphy for diagnosing and staging carcinoid tumours: correlations with the pathological indexes p53 and Ki-67. Nucl Med Commun 2002;23:727–34.
34. Adams S, Baum R, Rink T, et al. Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. Eur J Nucl Med 1998;25(1):79–83.
35. Binderup T, Knigge U, Loft A, et al. ^{18}F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res 2010;16(3):978–85.
36. Garin E, Le JF, Devillers A, et al. Predictive value of ^{18}F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. J Nucl Med 2009;50:858–64.
37. Zhang J, Liu Q, Singh A, et al. Prognostic value of (18) F-FDG PET/CT in a large cohort of 495 patients with advanced metastatic neuroendocrine neoplasms (NEN) treated with peptide receptor radionuclide therapy (PRRT). J Nucl Med 2020;61(11):1560–9.
38. Pavel M, Hainsworth JD, Baudin E, et al. A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus plus octreotide LAR vs placebo plus octreotide LAR in patients with advanced neuroendocrine tumors (NET) (RADIANT-2). Ann Oncol 2010;21(Suppl 8):viii4.
39. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656–63.
40. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of (177)Lu-Dotatate for Midgut neuroendocrine tumors. N Engl J Med 2017;376:125–35.
41. Gabriel M, Nilica B, Kaiser B, et al. Twelve-year follow-up after peptide receptor radionuclide therapy (PRRT). J Nucl Med 2018. https://doi.org/10.2967/jnumed.118.215376.
42. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3] octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124–30.
43. Virgolini I, The Innsbruck Team. Peptide receptor radionuclide therapy (PRRT): clinical significance of re-treatment? Eur J Nucl Med Mol Imaging 2015;42:1949–54.
44. Prasad V, Horsch D, Hommann M, et al. Survival benefits and efficacy of peptide receptor radionuclide therapy (PRRT) using Y-90/Lu-177 DOTATATE in pancreatic neuroendocrine tumors (pNET) [abstract]. J Nucl Med 2009;50(suppl 2):43.
45. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine tumors. Pancreas 2017;46:707–14.
46. Forrer F, Uusijarvi H, Storch D, et al. Treatment with ^{177}Lu-DOTATOC of patients with relapse of neuroendocrine tumors after treatment with ^{90}Y-DOTA-TOC. J Nucl Med 2005;46:1310–6.
47. Khan S, Krenning EP, van Essen M, et al. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med 2011;52:1361–8.
48. Marinova M, Mucke M, Mahlberg L, et al. Improving quality of life in patients with pancreatic neuroendocrine tumor following peptide receptor radionuclide

therapy assessed by EORTC QLQ-C30. Eur J Nucl Med Mol Imaging 2018;45:38–46.

49. Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with (177)Lu-Dotatate in the phase III NETTER-1 trial. J Clin Oncol 2018;36:2578–84.
50. Martini C, Buxbaum S, Rodrigues M, et al. Quality of life in patients with metastatic gastroenteropancreatic neuroendocrine tumors receiving peptide receptor radionuclide therapy: information from a monitoring program in clinical routine. J Nucl Med 2018;59:1566–73.
51. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging 2015;42(1):5–19.
52. Melis M, Krenning EP, Bernard BF, et al. Localisation and mechanism of renal retention of radiolabelled somatostatin analogues. Eur J Nucl Med Mol Imaging 2005;32(10):1136–43.
53. Nilica B, Svirydenka H, Fritz J, et al. Nephrotoxicity and hematotoxicity one year after four cycles of peptide receptor radionuclide therapy (PRRT). J Nucl Med 2020;61(suppl 1):307–12.
54. Kong G, Callahan J, Hofman MS, et al. High clinical and morphologic response using ^{90}Y-DOTA-octreotate sequenced with ^{177}Lu-DOTA-octreotate induction peptide receptor chemoradionuclide therapy (PRCRT) for bulky neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2017;44:476–89.