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Molecular imaging in neuroendocrine tumors: Recent advances, controversies, unresolved issues, and roles in management

Tetsuhide Ito[1] and **Robert T. Jensen**[2]

[1]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan

[2]Digestive Diseases Branch, NIDDK, NIH, Bethesda, MD, 20892-1804, USA

Abstract

Purpose—To review recent advances in molecular imaging of neuroendocrine tumors (NETs), discuss unresolved issues, and review how these advances are affecting clinical management.

Recent findings—Molecular imaging of NETs underwent a number of important changes in the last few years, leading to some controversies, unresolved issues, and significant changes in clinical management. The most recent changes are reviewed in this article. Particularly important is the rapid replacement in somatostatin receptor scintigraphy (SRS) of ^{111}In-DTPA-SPECT/CT by ^{68}Ga-DOTA-peptide-PET/CT imaging, which is now approved in many countries including the US. Numerous studies in many different types of NETs demonstrate the greater sensitivity of ^{68}Ga-DOTA-peptide-PET/CT, its high specificity, and its impact on management. Other important developments in SRS/molecular imaging include demonstrating the prognostic value of both ^{68}Ga-DOTA-peptide-PET/CT and ^{18}F-FDG –PET/CT; how their use can be complementary; comparing the sensitivities and usefulness of ^{68}Ga-DOTA-peptide-PET/CT and ^{18}F-FDOPA PET/CT; introducing new linkers and radiolabeled ligands such as ^{64}Cu-DOTA-peptides with a long half-life, enhancing utility; and the introduction of somatostatin receptor antagonists which show enhanced uptake by NETs. In addition, novel ligands which interact with other receptors (GLP1, Bombesin, CCK, GIP, integrin, chemokines) are described which show promise in the imaging of both NETs and other tumors.

Summary—Molecular imaging is now required for all aspects of the management of patients with NETs. It results are essential not only for the proper diagnostic management of the patient, but also for assessing whether the patient is a candidate for peptide receptor radionuclide therapy (PRRT) with ^{177}Lu and also for providing prognostic value.

Keywords

somatostatin; somatostatin-receptor scintigraphy; ^{68}Gallium PET/CT; Carcinoid; pancreatic neuroendocrine tumor

Correspondence to: Dr Robert T Jensen, National Institutes of Health, Bldg. 10, Room 9C-103, Bethesda, MD 20892-1804, robertj@bdg10.niddk.nih.gov, Phone: 301-496-4201.

Conflicts of Interest

None

Introduction

Neuroendocrine tumor (NET) is now the recommended term to include both pancreatic (neuro)endocrine tumors (pNETs/PETs) and NETs in other locations, including gastrointestinal NETs (GI-NETs) (carcinoids), comprising 70% of all NETs[1•]. NETs present many unique problems in their management, because they differ from adenocarcinomas in their pathogenesis, diagnosis, clinical presentations, and treatment approaches[1•, 2••, 3]. NETs are increasing in frequency in almost all countries and present two management problems: the management of the NET itself, because a proportion pursue aggressive growth, and management of the hormone excess-state which occurs in up 30% of pNETs and 3–13% of patients with GI-NETs (carcinoids)[3, 4]. Curative resection would treat both problems, however in many cases, because of the extent of disease, this is not possible, and therefore treatment must be directed at each of these two problems[3–5].

The steps in the management of patients with NETs include suspecting and establishing the diagnosis, determining whether an inherited genetic syndrome is present (MEN1, MEN2, VHL, NF1, etc.), controlling the hormone-excess state, assessing the location and extent of the tumor burden, assessing the histological features of the tumor (proliferative indices, degree of differentiation) and treatment of the tumor either medically or surgically[2••, 3, 5, 6]. An essential aspect of the management is tumor imaging to assess location and extent, which presents a number of unique features, not seen in other tumors[3, 7••, 8]. Particularly important in these tumors is the increasingly important role of molecular imaging. A number of recent reviews and other studies have covered various aspects of imaging including the important role of cross-sectional imaging (CT, MRI, Ultrasound), hormonal sampling, endoscopic procedures, and other localization methods unique to these tumors, including aspects of molecular imaging[3, 8–11, 12•, 13, 14]. Molecular imaging of NETs has been a particular active area of investigation and resulting in changes which are unique to NETs, but which also has widespread implications for other neoplasms[14–16]. This review will highlight recent advances in this area (Table 1), the controversies and unresolved issues that have arisen (Table 2), and how these affect management, focusing primarily on advances in the last 3–5 years.

Why imaging is important in NETs and frequently difficult

Accurate tumor imaging is essential to planning the approach in all phases of management of patients with NETs. First, surgical resection remains the only curative procedure and thus should be carried out whenever it can be safely undertaken and has a high promise of a curative result[2••, 3, 5, 7••, 17]. To increase the possibility of successful surgery and prevent unnecessary surgery, accurate information on the location of the primary tumor and extent of the disease prior to surgery is essential[2••, 3, 5, 7••, 17]. In patients with unresectible disease, accurate imaging is essential to determine timing of antitumor therapies, the response to treatment, and the possible need for new approaches during treatment[2••, 7••, 8]. In patients with hormone excess-states unresponsive to medical therapy, imaging studies are essential in planning possible cytoreductive surgery, chemotherapy or treatment modalities directed at liver-predominant disease (embolization,

chemoembolization, radioembolization), all of which have been successful in various series[18, 19].

Tumor imaging has been particularly difficult in a number of subgroups of patients with NETs. Patients with functional pNETs (F-pNETs) characteristically present with symptoms of the hormone excess-state[5, 6] with small primary tumors (<1 cm) which are frequently missed by conventional imaging studies. The success of cross-sectional imaging studies is very much affected by tumor size: detecting 10–30% of NETs <1–1.5 cm, whereas they detect >80% of those >3 cm[3, 5, 12•]. Measurments of hormonal gradients is more sensitive[•12, 20–22], but is usually performed with angiography (insulinomas, gastrinomas), is invasive and uncommonly performed nowadays, except to localize insulinomas in specialized centers in the uncommon patient when all other studies are negative, or in patients with MEN1[3, 12•]. Patients with GI-NETs (carcinoids) and carcinoid syndrome have liver metastases in >95% of cases at the time of presentation [3]. In some of these patients, as well as patients presenting with metastatic nonfunctional NETs, the primary tumor can be small and difficult to localize, but its localization is important in selecting the proper antitumor treatment[15, 23–26]. Lastly, both malignant pNETs as well as GI-NETs frequently metastasize to adjacent lymph nodes, which are not seen on cross-sectional imaging and which can be difficult to localize at surgery[5, 17, 27]. Each of these points argue for the need for more sensitive imaging modalities in patients with NETs.

Molecular imaging of neuroendocrine tumors

General aspects

There are a number of molecular imaging approaches for NETs that are increasingly being used. These include somatostatin-receptor scintigraphy (SRS) using ligands that are targeted to somatostatin-receptors (primarily sst2) overexpressed by NETs[7••, 28]. This method is now approved in many countries including the United States and utilizes primarily ^{111}In-DPTA-peptides, with SPECT/CT-imaging or using ^{68}Ga-DOTA-peptides with positron emission tomography (PET) combined with CT-imaging (PET/CT) or magnetic resonance imaging (PET/MRI)[7••, 8, 29•, 30–32]. Other molecular imaging approaches include the use of ^{18}F-FDG with PET/CT imaging which assesses glucose uptake by tumors[8, 29•, 31, 32, 33•]; ^{125}I-MIBG(^{123}I-metaiodobenyzl-guanidine)-scintigraphy which utilitizes an analogue of guanidine, which is taken up by cells of sympathomedullary tissues and retained intracellularly by storage in catecholamine storage granules[8, 29•, 32]; and the use of ^{18}F-DOPA(^{18}F-dihydroxyphenylalanine)PET or ^{11}C-5-hydroxy-L-tryptophan(5-HTP)(^{11}C-5-HTP)- PET which takes advantage of the fact that NETs take up and decarboxylate amine precursors[8, 29•, 31, 32, 34]. ^{11}C-5-hydroxy-L-tryptophan(5-HTP)(^{11}C-5-HTP)-PET/CT is rarely used and only available in a few clinical centers.

Initially, beginning in the 1990s the most widely used approach was SRS with ^{111}In-DPTA-labeled-somatostatin agonist analogues, which had high affinity primarily for the somatostatin receptor subtype sst2[8, 9, 35]. For well-differentiated NETs, 80–100% express at least one of the 5 somatostatin receptor subtypes (sst1-5), with the most frequent being sst2 (>80%).This approach has greater sensitivity than conventional imaging studies, generally ranging from 60–90% for both pNETs and GI-NETs[8, 9, 35–37]. It has proven

especially useful for allowing whole body imaging at one time and for detecting distant metastases, whereby its use resulted in management changes in 25–50% of cases[35, 38, 39]. This approach is limited by the size of NET (identify <50% <1 cm)[8, 40] and by the degree of differentiation of the NET, because poorly differentiated tumors frequently either do not express somatostatin receptors or do so only at low densities[8, 35, 36]. However, this aproach allows an assessment of magnitude of uptake by the tumor and establishes the presence of somatostatin-receptors in the NET, which can be used to plan therapy with other radiolabeled-somatostatin analogues(^{90}Y-,^{177}Lu-labeled-analogues), using peptide receptor radionuclide radiotherapy (PRRT)[8, 35, 36].

PRRT will not be generally discussed in this review, however, it is receiving much attention as a therapeutic, targeted approach for patients with advanced NETs, and thus plays a role in the utilization of SRS, to assess whether this approach might be considered, by establishing the presence of somatostatin receptors on NET tissue [30, 32, 35, 41••, 42]. A recent prospective, randomized clinical trial (NETTER)[43•] using ^{177}Lu-DOTATATE in patients with unresectable advanced ileal NETs has been reported in preliminary communications to be effective with an acceptable safety profile. Therefore the availability of PRRT in the future will be a major factor in determining the use of SRS.

Over the last 3–5 years there have been considerable advances in molecular imaging of NETs, both in describing new approaches, new ligands, as well as comparison of different methods and studies leading to a better definition of their potential place in standard medical practice (Table 1). In some cases this had led to controversies and unresolved issues (Table 2) and changes in clincial management. These will be briefly reviewed in the following sections.

Rise of ^{68}Ga-DOTA-peptide-PET/CT imaging

Molecular imaging with ^{68}Ga-DOTA-labeled-somatostatin analogues has a number of advantages over imaging with ^{111}In-DTPA-peptide-SPECT/CT and is now becoming the standard, which is recommended in most current guidelines and is approved in many countries, including recently in the United States[2••, 5, 7••, 8, 29•, 31, 44–47]. The use of ^{68}Ga allows PET-imaging with greater spatial resolution(0.5 cm vs 1.5 cm for ^{111}In-DTPA-peptides/SPECT); has a shorter half-life of 68 min, allowing rapid scanning (1–3 hrs post injection versus 24–48 hr for ^{111}In); it is produced from a generator rather than a cyclotron; its effective dose is less than onehalf of that using ^{111}In-DTPA-peptides and the tissue contrast is better with PET/CT than with SPECT/CT-imaging[7••, 36, 46].

There are numerous recent studies [48••, 49–54] demonstrating imaging superiority of ^{68}Ga-DOTA-labeled-somatostatin analogues in patients with various NETs over conventional cross-sectional imaging studies and SRS with ^{111}In-DTPA-peptides with SPECT/CT-imaging. These recent studies support the superiority of ^{68}Ga-DOTA-PET/CT in pNETs/GI-NETs (carcinoids) [48••, 49–54] in MEN1 patients[12•, 49], in head and neck paragangliomas[55, 56], medullary thyroid cancer[50], pheochromocytomas[56, 58], and ectopic Cushing's syndrome[57]. Furthermore, a meta-analysis in 2012[59] involving 16 studies (567 NET patients including patients with thoracic NETs) reported a sensitivity of 93% on a per-lesion basis (91% per-patient basis) with excellent specificity. A more recent

meta-analysis[48] summarizing 42 studies supported the superiority of ^{68}Ga-DOTA-PET/CT over conventional imaging or ^{111}In-DTPA-SPECT/CT demonstrating a high sensitivity (90%), specificity (91%), and its safety. Occasional false-negatives were observed and occurred primarily in poorly-differentiated NETs or insulinomas that have no or low somatostatin receptor sst2 expression and with small lesions (<0.7 cm)[59]. During interpretation of the ^{68}Ga-DOTA-peptide-PET/CT images, numerous studies have pointed out false-positives can occur due to uptake in the uncinate process of the pancreas, the adrenal gland or due to high somatostatin receptor expression in the spleen and splenosis, with inflammatory processes, or with increased osteoblastic activity[60, 61]. The use of ^{68}Ga-DOTA-PET/CT has been reported to change clinical management in 20–70% of NET patients[62, 63, 64••, 65, 66•, 67, 68].

The uptake of ^{68}Ga-DOTA-peptides by NETs strongly correlates with the tumor expression of sst2[50, 69, 70]. A number of recent studies[53, 71–74]have reported that the maximum standardized uptake value(SUV/max) of ^{68}Ga-DOTA-peptide-PET/CT-imaging of NETs has important prognostic and predictive value. In well-differentiated NETs it was an independent predictor of progression-free survival(PFS)[53, 74]. In another study[71] a cutoff-value of 16.4 for ^{68}Ga-DOTA-peptide-PET/CT was found predictive of a tumor response with PRRT using either ^{90}Y- or ^{177}Lu-labeled somatostatin analogues. SUV/max on ^{68}Ga-DOTA-peptide-PET/CT has also been reported to be predictive in patients with advanced NETs regarding their response to octreotide therapy with a SUV/MAX>29.4 associated with a longer PFS[72]. In patients with well-differentiated G1/G2 pNETs[73], a SUV/Max >37.8 on ^{68}Ga-DOTA-peptide-PET/CT was an independent predictor of PFS.

Three different ^{68}Ga-linker-somatostatin labeled analogues have been used in different studies including ^{68}Ga-DOTATATE (the most commonly used), ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC[47, 50, 75]. These differ in their affinities for the different somatostatin receptor subtypes (sst1-5), but all have high affinity for sst2. Each of these performs better than SRS with ^{111}In-DTPA-peptide-SPECT/CT[32, 47, 75]. They have been directly compared in relatively few studies with one suggesting uptake was better with ^{68}Ga-DOTATATE[76] and a second reported the sst2,3,5-specific ^{68}Ga-DOTANOC detected more lesions[75]. Reviews of all studies comparing these different ligands concluded that overall there seemed to be no or little major difference in their performance[32, 47].

Comparison of ^{68}Ga-DOTA-PET/CT and ^{18}F-FDG-PET/CT

Whereas ^{68}Ga-DOTA-peptide-PET/CT assesses NET somatostatin receptor expression, ^{18}F-FDG-PET/CT studies metabolic-activity by assessing glucose-uptake, and therefore these two imaging modalities assess different characteristics of NETs. Older studies suggested that ^{18}F-FDG-PET/CT had minimal utility in NETs, however, more recent studies show a percentage of NETs have high ^{18}F-FDG-PET/CT activity[74, 77–84]. Recently there have been a number of studies attempting to define the potential usefulness of ^{18}F-FDG-PET/CT and ^{68}Ga-DOTA-peptide-PET/CT either alone or together[74, 77, 79, 80]. In general, these studies support the conclusion that ^{68}Ga-DOTA-peptide-PET/CT demonstrated superior imaging in well-differentiated G1/G2 NETs compared to ^{18}F-FDG-PET/CT, whereas ^{18}F-FDG-PET/CT demonstrates higher uptake in poorly-differentiated G3 NETs than ^{68}Ga-

DOTA-peptide-PET/CT[77, 79]. A similar pattern is seen with lung carcinoids with ^{68}Ga-DOTA-peptide-PET/CT being more sensitive than ^{18}F-FDG-PET/CT for detecting typical carcinoids, whereas the reverse was true for atypical lung carcinoids[85•]. The presence of ^{18}F-FDG-PET/CT in NETs has been shown to correlate strongly with high rate of progression and to have prognostic significance[77, 78, 81, 83, 84]. In one study patients with a positive ^{18}F-FDG-PET/CT with a SUV ratio of 2.5 of greater had a 4-yr survival rate of 0%[81]. Furthermore, in a number of studies, some patients with G1/G2 tumors had positive ^{18}F-FDG-PET/CT uptake which had important predictive value[33•, 77, 82]. A number of studies have concluded that the results of ^{18}F-FDG-PET/CT and ^{68}Ga-DOTA-peptide-PET/CT in patients with NETs are complementary in providing different information that is clinically relevant[77, 79, 80]. In one study their combined impact was to change the therapeutic decision in 59% of the patients[79].

In well-differentiated NETs the maximal standardized uptake value (SUV/Max) for ^{68}Ga-DOTA-PET/CT is superior to that for ^{18}F-FDG-PET/CT as an independent prognostic factor for PFS[53].

SRS with ^{111}In-DPTA-SPECT/CT has also been compared to ^{18}F-FDG-PET/CT in studies[81, 82, 86]. Similar, although less dramatic results compared with those seen with the comparison of ^{68}Ga-DOTA-PET/CT and ^{18}F-FDG-PET/CT reviewed above, were obtained. SRS with ^{111}In-DPTA-peptide-SPECT/CT had greater sensitivity for well-differentiated NETs than ^{18}F-FDG-PET/CT, and the reverse was true for poorly-differentiated NETs[82]. The sensitivity of ^{111}In-DPTA-peptide-SPECT/CT and ^{18}F-FDG-PET/CT were very much affected by the tumor grade, being 79% vs 52% for Grade 1, 85% vs 86% for Grade 2, and 57% vs 100% for Grade 3[82]. ^{111}In-DPTA-peptide-SPECT/CT negativity and ^{18}F-FDG-PET/CT positivity correlate with early tumor progression[86], and ^{18}F-FDG-PET/CT positivity[78, 86] correlated with shortened PFS and overall survival.

Comparison of ^{68}Ga-DOTA-PET/CT and ^{18}F-FDOPA PET/CT

^{18}F-FDOPA PET/CT takes advantage of the fact that NETs take up and decarboxylate amine precursors by assessing the ability of the tumor cells to be taken up by a neutral-amino acid-transporter (LAT1/4F2hc)[87•]. In contrast, ^{68}Ga-DOTA-peptide-PET/CT assesses NET somatostatin receptor expression, and therefore, these two imaging modalities assess different characteristics of NETs. A number of studies have recently compared these two radiolabeled peptides in patients with different NETs[56]. In patients with pheochromocytomas and paragangliomas, ^{68}Ga-DOTA-peptide-PET/CT is more sensitive than 18F-FDOPA-PET/CT in detecting head and neck paragangliomas, especially in patients with SDHD (succinate dehydrogenase-subunit b mutations)[56]. ^{18}F-FDOPA-PET/CT is reported to be a good modality for detecting medullary thyroid cancer, investigating hyperinsulinemic states, and is more sensitive than SRS with ^{111}In-DTPA-SPECT/CT in detecting and staging carcinoid tumors, but not pNETs[8, 34, 87•, 88].

In one comparative study ^{18}F-FDOPA PET/CT was less sensitive than ^{68}Ga-DOTA-peptide-PET/CT in detecting NETs((70% pNETs)[89].

Similar to ^{68}Ga-DOTA-peptide-PET/CT, ^{18}F-FDOPA PET/CT is of limited value in localizing insulinomas[46, 90–92]. Carbidopa is an inhibitor of peripheralaromaticamino-acid decarboxylase, and its administration has been shown to increase the sensitivity of ^{18}F-FDOPA PET/CT detection of insulinomas to 70%[93]. In another study[94] carbidopa premedication increased the sensitivity of ^{18}F-FDOPA PET/CT to 90% for localizing NF-pNETs, which was superior to the 68% seen with ^{111}In-DTPA-SPECT/CT-imaging.

Use of radiolabeled antagonists rather than agonists

Initially only radiolabeled somatostatin receptor agonists were used for SRS/PRRT because it was assumed that cellular internalization of ligand by the tumor was essential for both imaging and for PRRT, because with numerous G-protein-coupled receptors, peptide agonists, but not antagonists are internalized[95, 96]. However, in preclinical studies in animals, ^{111}In labeled sst2/sst3 peptide receptor antagonists showed superior binding in both amount and in retention-time with cells expressing these receptors, than seen with ^{111}In-labeled-agonists[96], even though the antagonists were not internalized. Analysis of the binding characteristics demonstrated the antagonist showed a 10-times higher number of binding sites than seen with the agonist[96], possibly because it was interacting with predominately low-affinity receptor-sites ,whereas the agonist may have interacted with predominately high-affinity receptor-states.

Subsequently, in a study of 5 patients with metastatic thyroid cancers or NETs[95], a radiolabeled-antagonist, ^{111}In-DOTA-BASS, showed higher tumor-uptake and lower renal retention than the radiolabeled-agonist, and imaged more lesions.

These promising results have been extended to the investigation of the relative value of radiolabeled-somatostatin analogues that are agonists or antagonists, for their tumoricidal effects on sst2-containing tumor cells by PRRT[97]. In a preclinical study the radiolabeled antagonist, ^{177}Lu-DOTA-JR11, demonstrated 5-times greater tumor cell-associated radioactivity than the agonist, ^{177}Lu-DOTA-octreotate, caused more double-stranded DNA breaks in the tumor, showed in biodistribution studies a 4-times greater radiation-dose with the antagonist and in an in vivo study, and resulted in a longer tumor-growth delay. These promising results were extended recently to investigate the comparative effect of these two ligands for PRRT in 4 patients with advanced NETs[98••]. ^{177}Lu-DOTA-JR11 delivered 1.7–10.6-fold higher tumor doses than ^{177}Lu-DOTATATE, and the tumor-kidney and tumor to bone marrow dose was 1.1–7.2 times higher. The radiolabeled antagonist caused a partial remission in 2/4 patients, stable disease in 1 patient and a mixed response in the 4th patient[98••]. These results demonstrate that radiolabeled-somatostatin receptor antagonists show promise of being superior agents to the currently widely used radiolabeled-agonists, for both imaging and for PRRT.

Development of other radiolabeled ligands for imaging

^{68}Ga has a short half-life of 68 min which can lead to logistic problems with many patients examined daily and it has a limited spatial resolution, which can be overcome by the use of ^{64}Cu (half-life −12.7 hrs), allowing once-daily preparation for multiple uses, and it has lower positron energy than ^{68}Ga which should translate into better spatial resolution[99–

101]. In 14 patients with NETS ^{64}Cu-DOTATATE imaging was investigated using both SPECT/CT and PET/CT[100]. Images of excellent quality with high spatial resolution were obtained and in 43% of patients additional lesions were found using PET/CT compared to SPECT/CT[100]. In a second study[99] ^{64}Cu-DOTATATE-PET/CT was compared prospectively to ^{111}In-DTPA-Octreotide in 112 patients with confirmed NETs. The diagnostic sensitivity of ^{64}Cu-DOTATATE-PET/CT was 97%/97% which was significantly better than ^{111}In-DTPA-Octreotide(87%/87%) and with ^{64}Cu-DOTATATE-PET/CT twice as many lesions were detected including in 36% of patients in organs thought not involved by ^{111}In-DTPA-Octreotide imaging[99]. A recent study [102••] reports a prospective, head-to-head comparison of ^{64}Cu-DOTATATE-PET/CT and ^{68}Ga-DOTATATE-PET/CT in 59 NET patients and found they had equal sensitivity on a per patient-basis, but ^{64}Cu-DOTATATE-PET/CT identified significantly more lesions and its longer half-life made it easier to use in a clinical setting.

A preclinical study reports[103]excellent imaging of HEK-sst2 containing xenografts by two sst2-radiolabeled antagonists, ^{64}Cu- and ^{68}Ga-NODAGA-LM3. The authors conclude that these ligands are promising candidates for imaging with favorable pharmacokinetics and high-image contrast on PET/CT[103].

Using somatostatin receptor overexpression to deliver cytotoxic doses of radiolabeled somatostatin receptor ligands(PRRT) has received the most attention using β-emitting isotopes(^{90}Y,^{177}Lu), however a significant number of patients do not show tumor shrinkage and new approaches are being considered. One approach is to use ^{213}Bi-DOTATOC, which allows target alpha-particle therapy[104]. In one study of 7 patients refractory to ^{90}Y/^{177}Lu-DOTATATE, all demonstrated enduring responses with favorable acute and midterm toxicity with ^{213}Bi-DOTATOC[104]. Other approaches being taken to increase the cytotoxicity of ^{90}Y-/^{177}Lu in PRRT include the use of combination therapies including using ^{90}Y-/^{177}Lu-DOTATATE together[105]; combined with PARP inhibitors to potentiate the accummulation of double-stranded DNA breaks and cytoxicity[106]; with peptide-degradation inhibitors such as phosphoramidon to increase tissue uptake[107, 108] or with chemotherapeutics to increase sensitivity such as temozolomide, or capecitabine and other anti-tumor agents such as everolimus[30, 109–112].

Novel ligands and approaches

In addition to ligands for somatostatin receptors, a number of other molecular imaging probes are in development, which may prove to be useful not only in NETs, but also a wide group of other tumors. These include: radiolabeled GLP-1 receptor ligands[90, 113•, 114] which show particular promise in imaging insulinomas and adult nesidioblastosis; radiolabeled-agonists interacting with the chemokine-receptor, CXCR4, which is frequently overexpressed in proliferating and advanced tumors including SCLC cells and NETs[16, 115]; ^{68}Ga-DOTA-labeled CCK2 receptor ligands for imaging medullary thyroid cancer and SCL cancer[116–118]; radiolabeled-bombesin receptor ligands (agonists/ antagonists)(BB1, BB2,BB3-receptor) which can image a large range of tumors (prostate, colon, breast, CNS, NETs)[15, 119•]; radiolabeled-ligands which interact with VIP-PACAP receptors (VPAC1,VPAC2,PAC) which also can image a wide range of tumors[120•], and

radiolabeled-ligands interacting with the glucose-dependent insulinotrophic-polypeptide receptor(GIPR) which is overexpressed by a number of tumors including NETs and whose expression correlates with the proliferative-index ,whereas sst expression does not[121–126]. A recent study demonstrated that a combination of GIP, somatostatin, and GLP-1 agonists identified all NETs, because at least one is overexpressed by all tumors and therefore it was proposed, triple peptide receptor targeting (GIPR, sst, GLP1R) should be considered for enhanced sensitivity[121, 123]. An additional area of molecular imaging receiving increased attention is the targeting of tumor's angiogenesis, including NETs, which are vascular tumors, using increased expression of integrin-receptors[127, 128•, 129–132].

Conclusion

Molecular imaging by performing somatostatin receptor scintigraphy(SRS) (using ^{111}In-DTPA-peptide-SPECT/CT or ^{68}Ga-DOTA-peptide-PET/CT) is now an essential component in almost all steps in the management of patients with NETs. Both are approved in the US and many countries. However, numerous studies now demonstrate in many different types of NETs, that ^{68}Ga-DOTA-peptide-PET/CT is the preferred modality because of its greater sensitivity, excellent specificity, better resolution and its use changes patient management in 20–70% of cases. Recent studies demonstrate that ^{68}Ga-DOTA-peptide-PET/CT also has prognostic value and that it and ^{18}F-FDG -PET/CT can be complementary. Recent studies have helped to define the role of ^{18}F-FDOPA PET/CT and reported novel ligands for SRS which show promise, include antagonists, which show enhanced imaging of NETs. Furthermore, other molecular receptor ligands for imaging are being studied (CCK, GLP1, GIP, chemokines, integrins, bombesin) which show promise in both NETs and other tumors.

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References

1. Klimstra DS. Pathologic Classification of Neuroendocrine Neoplasms. Hematol Oncol Clin North Am. 2016; 30:1–19. [PubMed: 26614366] •Recent review of the pathology of NETs including the grading system which is referred to frequently in paper
2. ENETS 2016 Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors: An Update. Neuroendocrinology. 2016; 103:1–194. [PubMed: 27710961] ••Most current ENETs consensus statements for managing all aspects of NETs
3. Jensen, RT.; Norton, JA.; Oberg, K. Neuroendocrine Tumors. In: Feldman, M.; Friedman, LS.; Brandt, LJ., editors. Sleisenger and Fordtran's Gastrointestinal and Liver Diseases. tenth. Philadelphia: Elsevier Saunders; p. 501-541.16 A.D
4. Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. Expert Opin Pharmacother. 2016:1–15.
5. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016; 103:153–171. [PubMed: 26742109]

6. Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: Advances. Best Pract Res Clin Gastroenterol. 2012; 26:737–753. [PubMed: 23582916]
7. Oberg K, Sundin A. Imaging of Neuroendocrine Tumors. Front Horm Res. 2016; 45:142–151. [PubMed: 27002535] •• Current general review of all aspects of imaging of NETs including molecular imaging
8. Toumpanakis C, Kim MK, Rinke A, et al. Combination of cross-sectional and molecular imaging studies in the localization of gastroenteropancreatic neuroendocrine tumors. Neuroendocrinology. 2014; 99:63–74. [PubMed: 24458014]
9. Krampitz GW, George BM, Willingham SB, et al. Identification of tumorigenic cells and therapeutic targets in pancreatic neuroendocrine tumors. Proc Natl Acad Sci U S A. 2016; 113:4464–4469. [PubMed: 27035983]
10. Pellicano R, Fagoonee S, Altruda F, et al. Endoscopic imaging in the management of gastroenteropancreatic neuroendocrine tumors. Minerva Endocrinol. 2016; 41:490–498. [PubMed: 27600643]
11. Krudy AG, Doppman JL, Jensen RT, et al. Localization of islet cell tumors by dynamic CT: Comparison with plain CT, arteriography, sonography and venous sampling. Am J Roentgenol. 1984; 143:585–589. [PubMed: 6087646]
12. Ito T, Jensen RT. Imaging in multiple endocrine neoplasia type 1: recent studies show enhanced sensitivities but increased controversies. Int J Endocr Oncol. 2016; 3:53–66. [PubMed: 26834963] •Recent review of the role/controversies of the use of molecular imaging in MEN1 patients
13. De Angelis C, Manfre SF, Bruno M, et al. Hegemony and cost-effectiveness of endoscopic ultrasound (EUS) in the field of gastroenteropancreatic-neuroendocrine tumors (GEP-NETs). Minerva Med. 2014; 105:363–370. [PubMed: 25325565]
14. Reubi JC. Old and new peptide receptor targets in cancer: future directions. Recent Results Cancer Res. 2013; 194:567–576. [PubMed: 22918784]
15. Sancho V, Di Florio A, Moody TW, et al. Bombesin receptor-mediated imaging and cytotoxicity: review and current status. Curr Drug Deliv. 2011; 8:79–134. [PubMed: 21034419]
16. Korner M. Specific biology of neuroendocrine tumors: Peptide receptors as molecular targets. Best Pract Res Clin Endocrinol Metab. 2016; 30:19–31. [PubMed: 26971841]
17. Tamburrino D, Spoletini G, Partelli S, et al. Surgical management of neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab. 2016; 30:93–102. [PubMed: 26971846]
18. Ito T, Igarashi H, Jensen RT. Therapy of metastatic pancreatic neuroendocrine tumors (pNETs): recent insights and advances. J Gastroenterol. 2012; 47:941–960. [PubMed: 22886480]
19. Prakash L, Bhosale P, Cloyd J, et al. Role of Fluorouracil, Doxorubicin, and Streptozocin Therapy in the Preoperative Treatment of Localized Pancreatic Neuroendocrine Tumors. J Gastrointest Surg. 2016
20. Doppman JL, Miller DL, Chang R, et al. Gastrinomas: localization by means of selective intraarterial injection of secretin. Radiology. 1990; 174:25–29. [PubMed: 2294556]
21. Cherner JA, Doppman JL, Norton JA, et al. Selective venous sampling for gastrin to localize gastrinomas. A prospective study. Ann Intern Med. 1986; 105:841–847. [PubMed: 3535602]
22. Morera J, Guillaume A, Courtheoux P, et al. Preoperative localization of an insulinoma: selective arterial calcium stimulation test performance. J Endocrinol Invest. 2016; 39:455–463. [PubMed: 26577133]
23. Maxwell JE, Sherman SK, Stashek KM, et al. A practical method to determine the site of unknown primary in metastatic neuroendocrine tumors. Surgery. 2014; 156:1359–1366. [PubMed: 25456909]
24. Imperiale A, Rust E, Gabriel S, et al. 18F-fluorodihydroxyphenylalanine PET/CT in patients with neuroendocrine tumors of unknown origin: relation to tumor origin and differentiation. J Nucl Med. 2014; 55:367–372. [PubMed: 24343986]
25. Alonso O, Rodriguez-Taroco M, Savio E, et al. (68)Ga-DOTATATE PET/CT in the evaluation of patients with neuroendocrine metastatic carcinoma of unknown origin. Ann Nucl Med. 2014; 28:638–645. [PubMed: 24862238]

26. Naswa N, Sharma P, Kumar A, et al. (6)(8)Ga-DOTANOC PET/CT in patients with carcinoma of unknown primary of neuroendocrine origin. Clin Nucl Med. 2012; 37:245–251. [PubMed: 22310250]
27. Krampitz GW, Norton JA, Poultsides GA, et al. Lymph nodes and survival in duodenal and pancreatic neuroendocrine tumors. Arch Surg. 2012; 147:820–827. [PubMed: 22987171]
28. Mikolajczak R, Maecke HR. Radiopharmaceuticals for somatostatin receptor imaging. Nucl Med Rev Cent East Eur. 2016; 19:126–132. [PubMed: 27479790]
29. Ambrosini V, Morigi JJ, Nanni C, et al. Current status of PET imaging of neuroendocrine tumours ([18F]FDOPA, [68Ga]tracers, [11C]/[18F]-HTP). Q J Nucl Med Mol Imaging. 2015; 59:58–69. [PubMed: 25677589] •Recent review of some important aspects of PET imaging in NET patients
30. Chatalic KL, Kwekkeboom DJ, de JM. Radiopeptides for Imaging and Therapy: A Radiant Future. J Nucl Med. 2015; 56:1809–1812. [PubMed: 26514175]
31. Baumann T, Rottenburger C, Nicolas G, et al. Gastroenteropancreatic neuroendocrine tumours (GEP-NET) - Imaging and staging. Best Pract Res Clin Endocrinol Metab. 2016; 30:45–57. [PubMed: 26971843]
32. Kjaer A, Knigge U. Use of radioactive substances in diagnosis and treatment of neuroendocrine tumors. Scand J Gastroenterol. 2015; 50:740–747. [PubMed: 25959100]
33. Panagiotidis E, Bomanji J. Role of 18F-fluorodeoxyglucose PET in the study of neuroendocrine tumors. PET Clin. 2014; 9:43–55. [PubMed: 25029933]
34. Balogova S, Talbot JN, Nataf V, et al. 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. Eur J Nucl Med Mol Imaging. 2013; 40:943–966. [PubMed: 23417499]
35. Teunissen JJ, Kwekkeboom DJ, Valkema R, et al. Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr Relat Cancer. 2011; 18(Suppl 1):S27–S51. [PubMed: 22005114]
36. Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab. 2007; 21:69–85. [PubMed: 17382266]
37. Gibril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas: a prospective study. Ann Intern Med. 1996; 125:26–34. [PubMed: 8644985]
38. Gibril F, Doppman JL, Reynolds JC, et al. Bone metastases in patients with gastrinomas: a prospective study of bone scanning, somatostatin receptor scanning, and MRI in their detection, their frequency, location and effect of their detection on management. J Clin Oncol. 1998; 16:1040–1053. [PubMed: 9508189]
39. Gibril F, Jensen RT. Diagnostic uses of radiolabelled somatostatin-receptor analogues in gastroenteropancreatic endocrine tumors. Dig Liver Dis. 2004; 36:S106–S120. [PubMed: 15077919]
40. Alexander HR, Fraker DL, Norton JA, et al. Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger-Ellison syndrome. Ann Surg. 1998; 228:228–238. [PubMed: 9712569]
41. Kwekkeboom DJ, Krenning EP. Peptide Receptor Radionuclide Therapy in the Treatment of Neuroendocrine Tumors. Hematol Oncol Clin North Am. 2016; 30:179–191. [PubMed: 26614376] •• Current review of all aspects of PRRT and role of molecular imaging in its use
42. Kim SJ, Pak K, Koo PJ, et al. The efficacy of (177)Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis. Eur J Nucl Med Mol Imaging. 2015; 42:1964–1970. [PubMed: 26253273]
43. Strosberg JR, Wolin EM, Chasen B, Kulke M, Bushnell DL, Caplin ME, Baum RP, Kunz PL, Hobday TJ, Hendifar AE, Oberg KE, Sierra ML, Kwekkeboom DJ, Ruszniewski PH, Krenning EP. NETTER-1 phase III: Progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroeneodcrine tumors treated with 177-Lu-Dotatate [abstract]. J Clin Oncol. 2016; 34:194. [PubMed: 26503197] •Preliminary communication of the results of first double-blind, controlled study of PRRT
44. Pavel M, O'Toole D, Costa F, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN)

and NEN of Unknown Primary Site. Neuroendocrinology. 2016; 103:172–185. [PubMed: 26731013]

45. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus Guidelines for the Management and Treatment of Neuroendocrine Tumors. Pancreas. 2013; 42:557–577. [PubMed: 23591432]
46. Ambrosini V, Nanni C, Fanti S. The use of gallium-68 labeled somatostatin receptors in PET/CT imaging. PET Clin. 2014; 9:323–329. [PubMed: 25030395]
47. Johnbeck CB, Knigge U, Kjaer A. PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. Future Oncol. 2014; 10:2259–2277. [PubMed: 25471038]
48. Deppen SA, Blume J, Bobbey AJ, et al. 68Ga-DOTATATE Compared with 111In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. J Nucl Med. 2016; 57:872–878. [PubMed: 26769864] ••Recent study showing superiority of 68Ga-DOTATATE over 111In-DTPA-Octreotide SPECT/CT
49. Morgat C, Velayoudom-Cephise FL, Schwartz P, et al. Evaluation of Ga-DOTA-TOC PET/CT for the detection of duodenopancreatic neuroendocrine tumors in patients with MEN1. Eur J Nucl Med Mol Imaging. 2016
50. Tran K, Khan S, Taghizadehasl M, et al. Gallium-68 Dotatate PET/CT is superior to other imaging modalities in the detection of medullary carcinoma of the thyroid in the presence of high serum calcitonin. Hell J Nucl Med. 2015; 18:19–24. [PubMed: 25679074]
51. Albanus DR, Apitzsch J, Erdem Z, et al. Clinical value of (6)(8)Ga-DOTATATE-PET/CT compared to stand-alone contrast enhanced CT for the detection of extra-hepatic metastases in patients with neuroendocrine tumours (NET). Eur J Radiol. 2015; 84:1866–1872. [PubMed: 26152870]
52. Goel R, Shukla J, Bansal D, et al. (68)Ga-DOTATATE positron emission tomography/computed tomography scan in the detection of bone metastases in pediatric neuroendocrine tumors. Indian J Nucl Med. 2014; 29:13–17. [PubMed: 24591776]
53. Sharma P, Arora S, Dhull VS, et al. Evaluation of Ga-DOTANOC PET/CT imaging in a large exclusive population of pancreatic neuroendocrine tumors. Abdom Imaging. 2015; 40:299–309. [PubMed: 25134801]
54. Deppen SA, Liu E, Blume JD, et al. Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors. J Nucl Med. 2016; 57:708–714. [PubMed: 26769865]
55. Janssen I, Chen CC, Taieb D, et al. 68Ga-DOTATATE PET/CT in the Localization of Head and Neck Paragangliomas Compared with Other Functional Imaging Modalities and CT/MRI. J Nucl Med. 2016; 57:186–191. [PubMed: 26564322]
56. Archier A, Varoquaux A, Garrigue P, et al. Prospective comparison of (68)Ga-DOTATATE and (18)F-FDOPA PET/CT in patients with various pheochromocytomas and paragangliomas with emphasis on sporadic cases. Eur J Nucl Med Mol Imaging. 2016; 43:1248–1257. [PubMed: 26637204]
57. Isidori AM, Sbardella E, Zatelli MC, et al. Conventional and Nuclear Medicine Imaging in Ectopic Cushing's Syndrome: A Systematic Review. J Clin Endocrinol Metab. 2015; 100:3231–3244. [PubMed: 26158607]
58. Janssen I, Blanchet EM, Adams K, et al. Superiority of [68Ga]-DOTATATE PET/CT to Other Functional Imaging Modalities in the Localization of SDHB-Associated Metastatic Pheochromocytoma and Paraganglioma. Clin Cancer Res. 2015; 21:3888–3895. [PubMed: 25873086]
59. Treglia G, Castaldi P, Rindi G, et al. Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. Endocrine. 2012; 42:80–87. [PubMed: 22350660]
60. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics. 2015; 35:500–516. [PubMed: 25763733]

61. Gibril F, Reynolds JC, Chen CC, et al. Specificity of somatostatin receptor scintigraphy: a prospective study and the effects of false positive localizations on management in patients with gastrinomas. J Nucl Med. 1999; 40:539–553. [PubMed: 10210211]
62. Srirajaskanthan R, Kayani I, Quigley AM, et al. The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. J Nucl Med. 2010; 51:875–882. [PubMed: 20484441]
63. 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; 56:40–47. [PubMed: 22339744]
64. Skoura E, Michopoulou S, Mohmaduvesh M, et al. The Impact of 68Ga-DOTATATE PET/CT Imaging on Management of Patients with Neuroendocrine Tumors: Experience from a National Referral Center in the United Kingdom. J Nucl Med. 2016; 57:34–40. [PubMed: 26471695] ••Recent study showing impact of 68Ga-DOTATATE on management
65. Ruf J, Heuck F, Schiefer J, et al. Impact of Multiphase 68Ga-DOTATOC-PET/CT on therapy management in patients with neuroendocrine tumors. Neuroendocrinology. 2010; 91:101–109. [PubMed: 19996582]
66. Panagiotidis E, Alshammari A, Michopoulou S, et al. Comparison of the impact of 68Ga-DOTATATE and 18F-FDG PET/CT on clinical management in patients with neuroendocrine tumors. J Nucl Med. 2016 (In press). •Recent study comparing impact of 68Ga-DOTATATE 18F-FDG PET/CT on clinical management
67. Ilhan H, Fendler WP, Cyran CC, et al. Impact of Ga-DOTATATE PET/CT on the Surgical Management of Primary Neuroendocrine Tumors of the Pancreas or Ileum. Ann Surg Oncol. 2014
68. Herrmann K, Czernin J, Wolin EM, et al. Impact of 68Ga-DOTATATE PET/CT on the management of neuroendocrine tumors: the referring physician's perspective. J Nucl Med. 2015; 56:70–75. [PubMed: 25500825]
69. Olsen IH, Langer SW, Federspiel BH, et al. (68)Ga-DOTATOC PET and gene expression profile in patients with neuroendocrine carcinomas: strong correlation between PET tracer uptake and gene expression of somatostatin receptor subtype 2. Am J Nucl Med Mol Imaging. 2016; 6:59–72. [PubMed: 27069766]
70. Lapa C, Hanscheid H, Wild V, et al. Somatostatin receptor expression in small cell lung cancer as a prognostic marker and a target for peptide receptor radionuclide therapy. Oncotarget. 2016; 7:20033–20040. [PubMed: 26936994]
71. Kratochwil C, Stefanova M, Mavriopoulou E, et al. SUV of [68Ga]DOTATOC-PET/CT Predicts Response Probability of PRRT in Neuroendocrine Tumors. Mol Imaging Biol. 2015; 17:313–318. [PubMed: 25319765]
72. Koch W, Auernhammer CJ, Geisler J, et al. Treatment with octreotide in patients with well-differentiated neuroendocrine tumors of the ileum: prognostic stratification with Ga-68-DOTA-TATE positron emission tomography. Mol Imaging. 2014; 13:1–10.
73. Ambrosini V, Campana D, Polverari G, et al. Prognostic Value of 68Ga-DOTANOC PET/CT SUVmax in Patients with Neuroendocrine Tumors of the Pancreas. J Nucl Med. 2015; 56:1843–1848. [PubMed: 26405169]
74. Sharma P, Naswa N, Kc SS, et al. Comparison of the prognostic values of Ga-DOTANOC PET/CT and F-FDG PET/CT in patients with well-differentiated neuroendocrine tumor. Eur J Nucl Med Mol Imaging. 2014
75. Wild D, Bomanji JB, Benkert P, et al. Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. J Nucl Med. 2013; 54:364–372. [PubMed: 23297077]
76. Kabasakal L, Demirci E, Ocak M, et al. Comparison of (6)(8)Ga-DOTATATE and (6)(8)Ga-DOTANOC PET/CT imaging in the same patient group with neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2012; 39:1271–1277. [PubMed: 22526963]
77. 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; 43:1585–1592. [PubMed: 26922350]

78. Binderup T, Knigge U, Loft A, et al. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res. 2010; 16:978–985. [PubMed: 20103666]

79. Has Simsek D, Kuyumcu S, Turkmen C, et al. Can complementary 68Ga-DOTATATE and 18F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? J Nucl Med. 2014; 55:1811–1817. [PubMed: 25315243]

80. Naswa N, Sharma P, Gupta SK, et al. Dual tracer functional imaging of gastroenteropancreatic neuroendocrine tumors using 68Ga-DOTA-NOC PET-CT and 18F-FDG PET-CT: competitive or complimentary? Clin Nucl Med. 2014; 39:e27–e34. [PubMed: 24217539]

81. Bahri H, Laurence L, Edeline J, et al. High prognostic value of 18F-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. J Nucl Med. 2014; 55:1786–1790. [PubMed: 25286923]

82. Squires MH III, Adsay NV, Schuster DM, et al. Octreoscan Versus FDG-PET for Neuroendocrine Tumor Staging: A Biological Approach. Ann Surg Oncol. 2015; 22:2295–2301. [PubMed: 25786743]

83. Ezziddin S, Adler L, Sabet A, et al. Prognostic stratification of metastatic gastroenteropancreatic neuroendocrine neoplasms by 18F-FDG PET: feasibility of a metabolic grading system. J Nucl Med. 2014; 55:1260–1266. [PubMed: 24876204]

84. Ianniello A, Sansovini M, Severi S, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18)F-FDG PET. Eur J Nucl Med Mol Imaging. 2016; 43:1040–1046. [PubMed: 26611427]

85. Lococo F, Perotti G, Cardillo G, et al. Multicenter comparison of 18F-FDG and 68Ga-DOTA-peptide PET/CT for pulmonary carcinoid. Clin Nucl Med. 2015; 40:e183–e189. [PubMed: 25608152] •Recent study comparing 68Ga-DOTATATE and 18F-FDG PET/CT in patients with pulmonary carcinoids

86. Garin E, Le JF, Devillers A, et al. Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. J Nucl Med. 2009; 50:858–864. [PubMed: 19443590]

87. Santhanam P, Taieb D. Role of (18) F-FDOPA PET/CT imaging in endocrinology. Clin Endocrinol (Oxf). 2014; 81:789–798. [PubMed: 25056984]

88. Minn H, Kemppainen J, Kauhanen S, et al. 18F-fluorodihydroxyphenylalanine in the diagnosis of neuroendocrine tumors. PET Clin. 2014; 9:27–36. [PubMed: 25029931]

89. Ambrosini V, Tomassetti P, Castellucci P, et al. Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. Eur J Nucl Med Mol Imaging. 2008; 35:1431–1438. [PubMed: 18418596]

90. Christ E, Wild D, Ederer S, et al. Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study. Lancet Diabetes Endocrinol. 2013; 1:115–122. [PubMed: 24622317]

91. Sharma P, Arora S, Karunanithi S, et al. Somatostatin receptor based PET/CT imaging with 68Ga-DOTA-Nal3-Octreotide for localisation of clinically and biochemically suspected insulinoma. Q J Nucl Med Mol Imaging. 2014

92. Tessonnier L, Sebag F, Ghander C, et al. Limited value of 18F-F-DOPA PET to localize pancreatic insulin-secreting tumors in adults with hyperinsulinemic hypoglycemia. J Clin Endocrinol Metab. 2010; 95:303–307. [PubMed: 19915018]

93. Imperiale A, Bahougne T, Goichot B, et al. Dynamic 18F-FDOPA PET Findings After Carbidopa Premedication in 2 Adult Patients With Insulinoma-Related Hyperinsulinemic Hypoglycemia. Clin Nucl Med. 2015; 40:682–684. [PubMed: 25549347]

94. Helali M, Addeo P, Heimburger C, et al. Carbidopa-assisted 18F-fluorodihydroxyphenylalanine PET/CT for the localization and staging of non-functioning neuroendocrine pancreatic tumors. Ann Nucl Med. 2016

95. Wild D, Fani M, Behe M, et al. First clinical evidence that imaging with somatostatin receptor antagonists is feasible. J Nucl Med. 2011; 52:1412–1417. [PubMed: 21852357]

96. Gurusamy KS, Ramamoorthy R, Sharma D, et al. Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases. Cochrane Database Syst Rev. 2009:CD007060. [PubMed: 19370671]

97. Dalm SU, Nonnekens J, Doeswijk GN, et al. Comparison of the therapeutic response to treatment with a 177-lutetium labeled somatostatin receptor agonist and antagonist in preclinical models. J Nucl Med. 2015

98. Wild D, Fani M, Fischer R, et al. Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. J Nucl Med. 2014; 55:1248–1252. [PubMed: 24963127]

99. Pfeifer A, Knigge U, Binderup T, et al. 64Cu-DOTATATE PET for Neuroendocrine Tumors: A Prospective Head-to-Head Comparison with 111In-DTPA-Octreotide in 112 Patients. J Nucl Med. 2015; 56:847–854. [PubMed: 25952736]

100. Pfeifer A, Knigge U, Mortensen J, et al. Clinical PET of neuroendocrine tumors using 64Cu-DOTATATE: first-in-humans study. J Nucl Med. 2012; 53:1207–1215. [PubMed: 22782315]

101. Anderson CJ, Dehdashti F, Cutler PD, et al. 64Cu-TETA-octreotide as a PET imaging agent for patients with neuroendocrine tumors. J Nucl Med. 2001; 42:213–221. [PubMed: 11216519]

102. Johnbeck CB, Knigge U, Loft A, et al. Head-to-head comparison of 64Cu-DOTATATE and 68Ga-DOTATOC PET/CT: a prospective study of 59 patients with neuroendocrine tumors. J Nucl Med. 2016 (In press). ••Study showing the potential advantages of using 64Cu-DOTATATE instead of 68Ga-DOTATOC PET/CT:

103. Fani M, Del Pozzo L, Abiraj K, et al. PET of somatostatin receptor-positive tumors using 64Cu- and 68Ga-somatostatin antagonists: the chelate makes the difference. J Nucl Med. 2011; 52:1110–1118. [PubMed: 21680701]

104. Kratochwil C, Giesel FL, Bruchertseifer F, et al. (2)(1)(3)Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol Imaging. 2014; 41:2106–2119. [PubMed: 25070685]

105. Seregni E, Maccauro M, Coliva A, et al. Treatment with tandem [(90)Y]DOTA-TATE and [(177)Lu] DOTA-TATE of neuroendocrine tumors refractory to conventional therapy: preliminary results. Q J Nucl Med Mol Imaging. 2010; 54:84–91. [PubMed: 20168290]

106. Nonnekens J, van Kranenburg M, Beerens CE, et al. Potentiation of Peptide Receptor Radionuclide Therapy by the PARP Inhibitor Olaparib. Theranostics. 2016; 6:1821–1832. [PubMed: 27570553]

107. Nock BA, Maina T, Krenning EP, et al. "To serve and protect": enzyme inhibitors as radiopeptide escorts promote tumor targeting. J Nucl Med. 2014; 55:121–127. [PubMed: 24287321]

108. Marsouvanidis PJ, Melis M, de Blois E, et al. In vivo enzyme inhibition improves the targeting of [177Lu]DOTA-GRP(13-27) in GRPR-positive tumors in mice. Cancer Biother Radiopharm. 2014; 29:359–367. [PubMed: 25286347]

109. Claringbold PG, Turner JH. Pancreatic Neuroendocrine Tumor Control: Durable Objective Response to Combination 177Lu-Octreotate-Capecitabine-Temozolomide Radiopeptide Chemotherapy. Neuroendocrinology. 2016; 103:432–439. [PubMed: 26065489]

110. Kamp K, Gumz B, Feelders RA, et al. Safety and efficacy of everolimus in gastrointestinal and pancreatic neuroendocrine tumors after (177)Lu-octreotate. Endocr Relat Cancer. 2013; 20:825–831. [PubMed: 24036133]

111. Kong G, Callahan J, Hofman MS, et al. High clinical and morphologic response using 90Y-DOTA-octreotate sequenced with 177Lu-DOTA-octreotate induction peptide receptor chemoradionuclide therapy (PRCRT) for bulky neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2016

112. Basu S, Ostwal V. The case for combined chemotherapy-peptide receptor radionuclide therapy (chemo-PRRT) strategy in metastatic neuroendocrine tumor: predicting and looking at the possible case scenarios. Eur J Nucl Med Mol Imaging. 2016

113. Antwi K, Fani M, Nicolas G, et al. Localization of Hidden Insulinomas with (68)Ga-DOTA-Exendin-4 PET/CT: A Pilot Study. J Nucl Med. 2015; 56:1075–1078. [PubMed: 25999434]

•Study showing the value of (68)Ga-DOTA-Exendin-4 PET/CT in patients with occult insulinomas

114. Christ E, Wild D, Antwi K, et al. Preoperative localization of adult nesidioblastosis using (6)(8)Ga-DOTA-exendin-4-PET/CT. Endocrine. 2015; 50:821–823. [PubMed: 26001537]
115. Lapa C, Luckerath K, Rudelius M, et al. [68Ga]Pentixafor-PET/CT for imaging of chemokine receptor 4 expression in small cell lung cancer--initial experience. Oncotarget. 2016; 7:9288–9295. [PubMed: 26843617]
116. Roosenburg S, Laverman P, Joosten L, et al. PET and SPECT imaging of a radiolabeled minigastrin analogue conjugated with DOTA, NOTA, and NODAGA and labeled with (64)Cu, (68)Ga, and (111)In. Mol Pharm. 2014; 11:3930–3937. [PubMed: 24992368]
117. Brom M, Joosten L, Laverman P, et al. Preclinical evaluation of 68Ga-DOTA-minigastrin for the detection of cholecystokinin-2/gastrin receptor-positive tumors. Mol Imaging. 2011; 10:144–152. [PubMed: 21439259]
118. Kaloudi A, Nock BA, Krenning EP, et al. Radiolabeled gastrin/CCK analogs in tumor diagnosis: towards higher stability and improved tumor targeting. Q J Nucl Med Mol Imaging. 2015; 59:287–302. [PubMed: 26158215]
119. Moreno P, Ramos-Alvarez I, Moody TW, et al. Bombesin related peptides/receptors and their promising therapeutic roles in cancer imaging, targeting and treatment. Expert Opin Ther Targets. 2016:1–19. •Review of potential uses of radiolabeled bombesin analogues for imaging/PRRT
120. Moody TW, Nuche-Berenguer B, Jensen RT. Vasoactive intestinal peptide/pituitary adenylate cyclase activating polypeptide, and their receptors and cancer. Curr Opin Endocrinol Diabetes Obes. 2016; 23:38–47. [PubMed: 26702849] •Review of potential uses of radiolabeled VIP/PACAP analogues for imaging/PRRT
121. Reubi JC, Waser B. Triple-peptide receptor targeting in vitro allows detection of all tested gut and bronchial NETs. J Nucl Med. 2015; 56:613–615. [PubMed: 25698785]
122. Gourni E, Waser B, Clerc P, et al. The glucose-dependent insulinotropic polypeptide receptor: a novel target for neuroendocrine tumor imaging-first preclinical studies. J Nucl Med. 2014; 55:976–982. [PubMed: 24744444]
123. Waser B, Rehmann R, Sanchez C, et al. Glucose-dependent insulinotropic polypeptide receptors in most gastroenteropancreatic and bronchial neuroendocrine tumors. J Clin Endocrinol Metab. 2012; 97:482–488. [PubMed: 22112810]
124. Korner M, Waser B, Reubi JC. Does somatostatin or gastric inhibitory peptide receptor expression correlate with tumor grade and stage in gut neuroendocrine tumors? Neuroendocrinology. 2015; 101:45–57. [PubMed: 25591947]
125. Sherman SK, Maxwell JE, Carr JC, et al. GIPR expression in gastric and duodenal neuroendocrine tumors. J Surg Res. 2014; 190:587–593. [PubMed: 24565507]
126. Sherman SK, Carr JC, Wang D, et al. Gastric inhibitory polypeptide receptor (GIPR) is a promising target for imaging and therapy in neuroendocrine tumors. Surgery. 2013; 154:1206–1213. [PubMed: 24238043]
127. Decristoforo C, Faintuch-Linkowski B, Rey A, et al. [99mTc]HYNIC-RGD for imaging integrin alphavbeta3 expression. Nucl Med Biol. 2006; 33:945–952. [PubMed: 17127166]
128. Chen H, Niu G, Wu H, et al. Clinical Application of Radiolabeled RGD Peptides for PET Imaging of Integrin alphavbeta3. Theranostics. 2016; 6:78–92. [PubMed: 26722375] •Review of potential uses of radiolabeled ligands interacting with integrin receptors for imaging
129. Oxboel J, Brandt-Larsen M, Schjoeth-Eskesen C, et al. Comparison of two new angiogenesis PET tracers 68Ga-NODAGA-E[c(RGDyK)]2 and (64)Cu-NODAGA-E[c(RGDyK)]2; in vivo imaging studies in human xenograft tumors. Nucl Med Biol. 2014; 41:259–267. [PubMed: 24417983]
130. Chakravarty R, Chakraborty S, Dash A. Molecular Imaging of Breast Cancer: Role of RGD Peptides. Mini Rev Med Chem. 2015; 15:1073–1094. [PubMed: 26349490]
131. Oxboel J, Schjoeth-Eskesen C, El-Ali HH, et al. (64)Cu-NODAGA-c(RGDyK) Is a Promising New Angiogenesis PET Tracer: Correlation between Tumor Uptake and Integrin alpha(V)beta(3) Expression in Human Neuroendocrine Tumor Xenografts. Int J Mol Imaging. 2012; 2012:379807. [PubMed: 23091717]

132. Cheng C, Pan L, Dimitrakopoulou-Strauss A, et al. Comparison between 68Ga-bombesin (68Ga-BZH3) and the cRGD tetramer 68Ga-RGD4 studies in an experimental nude rat model with a neuroendocrine pancreatic tumor cell line. EJNMMI Res. 2011; 1:34. [PubMed: 22214362]

KEY POINTS

- There have been numerous advances in Molecular imaging of NETs over the last few years.
- Molecular imaging in NET patients currently consists of somatostatin-receptor scintigraphy (using ^{111}In-DTPA-peptide-SPECT/CT ,^{68}Ga-DOTA-peptide-PET/CT)[approved in US/many countries]; ^{18}F-FDG -PET/CT; ^{18}F-FDOPA PET/CT; with less frequent general use of ^{125}I-MIBG or ^{11}C-5-hydroxy-L-tryptophan(5-HTP)(^{11}C-5-HTP)- PET/CT.
- ^{68}Ga-DOTA-peptide-PET/CT is rapidly replacing ^{111}In-DTPA-peptide-SPECT/CT because of its greater resolution resulting in greater sensitivity and changes in patient management.
- Recent studies have compared these different modalities, helping to define their place in management, which has resulted in some being complementary (^{68}Ga-DOTA-peptide-PET/CT/^{18}F-FDG) and also leading to some controversies and unresolved issues.
- Newer, novel ligands with different linkers and radiolabeles are being described include somatostatin-receptor antagonists which show enhanced imaging.
- Ligands for other receptors(CCK, GLP1, GIP, Bombesin, chemokines, integrins) are reported, that also show promise for imaging NETs and other tumors.

Table 1

Molecular imaging in Neuroendocrine tumors (NETs). Recent advances

1	Development of ^{68}Gallium(^{68}Ga)-labeled somatostatin analogues with PET/CT
2	Investigation of the role of ^{18}F-FDG PET/CT imaging either alone or combined with ^{68}Ga-peptide PET/CT
3	Studies of results of ^{18}F-DOPA (^{18}F-dihydroxyphenylalanine) PET/CT either alone or compared to ^{68}Ga-peptide PET/CT
4	Development of radiolabeled somatostatin receptor antagonists with enhanced sensitivity
5	Development of other, novel radiolabeled somatostatin receptor ligands: ^{64}Cu-labeled ligands for PET/CT; ligands with different linkers; alpha emitting ligands for enhanced Peptide radio-receptor therapy (PRRT)
6	Development of novel radiolabeled ligands interacting with other receptors for imaging NETs or other tumors: radiolabeled GLP-1 receptor ligands; CCK2 receptor ligands: Bombesin receptor ligands (BB_1, BB_2, BB_3); GIP receptor ligands and chemokine receptor CXCR4.

Table 2

Molecular imaging in Neuroendocrine tumors (NETs). Controversies/unresolved issues

1	What is current role of ^{18}F-FDG PET/CT imaging? Is it complementary enough to ^{68}Ga-peptide PET/CT that it should be routinely used? If not, in what subgroup?
2	Is there still a role for ^{111}In-DTPA-peptide-SPECT/CT or has it been completely replaced by ^{68}Ga-peptide PET/CT?
3	Is there still a role for ^{18}F-DOPA (^{18}F-dihydroxyphenylalanine) PET/CT or is it completely replaced by ^{68}Ga-peptide PET/CT?
4	Should ^{64}Cu-peptide PET/CT replace ^{68}Ga-peptide PET/CT?
5	What is the role of ^{68}Ga-labeled sst antagonist-PET/CT and should it replace ^{68}Ga-labeled-sst peptide agonist PET/CT?
6	What is the role of new, novel radiolabeled ligands interacting with other receptors for imaging NETs or other tumors: radiolabeled GLP-1 receptor ligands; CCK2 receptor ligands: Bombesin receptor ligands (BB_1, BB_2, BB_3); GIP receptor ligands and chemokine receptor CXCR4?