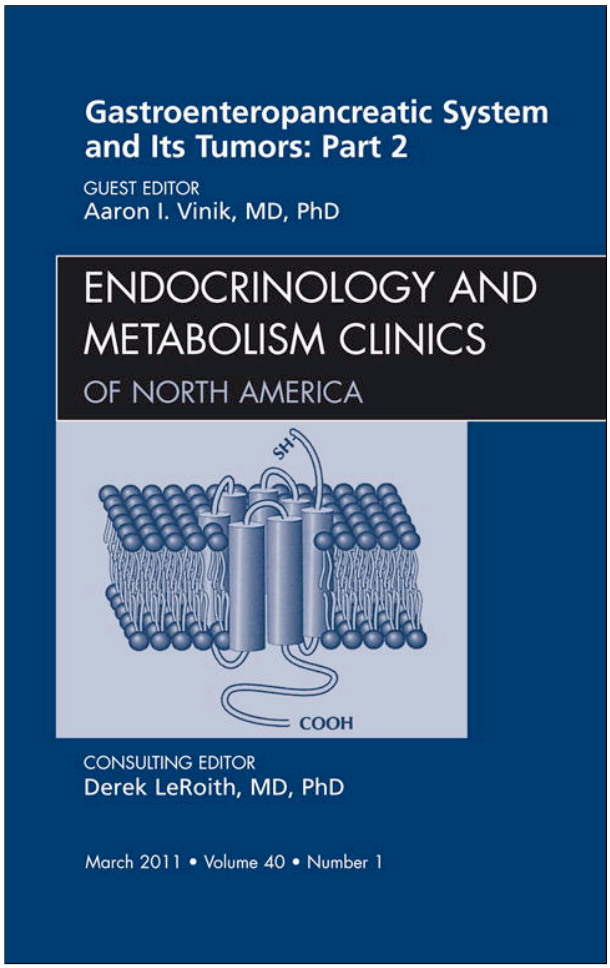

Standard Imaging Techniques for Neuroendocrine Tumors

David L. Bushnell, MD[a,b,*], Richard P. Baum, MD[c]

KEYWORDS

• Computed tomography • Magnetic resonance imaging
• Positron emission tomography • Neuroendocrine tumors

Several diagnostic imaging techniques including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)/CT, single-photon emission CT (SPECT), and SPECT/CT have been used successfully over the years in the evaluation of patients with neuroendocrine tumors (NET). Detection of distant disease and the primary tumor is critical for optimal management of patients with this malignancy.[1] This article reviews the various imaging methods and their respective advantages and limitations for use in different types of NETs and in particular carcinoid tumors. The reader is also referred for additional information to several excellent recent reviews on this subject.[2–5]

CT/MRI

CT and MRI are typically the initial imaging techniques used in the evaluation of most patients with suspected NETs both for the detection of the primary tumor and for detection of possible local or distant metastases. CT and MRI are fairly sensitive for detection of many types of primary NETs.[6] Sensitivity, however, may be limited in some cases for recurrent or metastatic disease. MRI appears to be more sensitive than CT for liver and bone marrow metastases, but small nodal metastases may be

The authors have nothing to disclose.
[a] Division of Nuclear Medicine, Department of Radiology, University of Iowa Roy J. and Lucille A. Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, USA
[b] Diagnostic Imaging and Radioisotope Therapy Service, Iowa City Veterans Administration Medical Center, Highway 6, Iowa City, IA 52244, USA
[c] Department of Nuclear Medicine/Center for Positron Emission Tomography, Pressekontakt: Katrin Gottwald, Zentralklinik Bad Berka GmbH, Robert-Koch-Allee 9, Bad Berka 99437, Germany
* Corresponding author. Division of Nuclear Medicine, Department of Radiology, University of Iowa Roy J. and Lucille A. Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242.
E-mail address: david-bushnell@uiowa.edu

Endocrinol Metab Clin N Am 40 (2011) 153–162
doi:10.1016/j.ecl.2010.12.002 **endo.theclinics.com**
0889-8529/11/$ – see front matter. Published by Elsevier Inc.

missed by either type of examination. Because these techniques primarily detect altered anatomy, they have only modest specificity.[6]

Most NETs are depicted on CT or MRI as enhancing lesions during the arterial phase of contrast delivery.[7] This is true for both the primary tumor and most metastases. Noncontrast images typically demonstrate low-density mass lesions on CT for either the primary or for metastases. Metastatic lesions often demonstrate low signal intensity on T1 weighted images versus high signal intensity on T2 weighted noncontrast images; however, there is significant patient-to-patient variability in this regard.[8] In general, multiphasic imaging, including the noncontrast phase, is required for optimal accuracy in this setting with either imaging method.[9]

SPECT/CT

The value of combining CT with SPECT in a single procedure cannot be overemphasized when imaging patients with the radiopharmaceuticals that will be discussed. When a SPECT/CT machine is not available, careful image correlation with standalone CT should be performed.[10]

Localization of a focus of uptake from either of these radiopharmaceuticals to a particular organ or structure in the body can mean the difference between a false-positive and a true-negative result. Moreover, at times subtle uptake that otherwise might be written off as insignificant may be deemed important by recognition of its location on CT. A good example of this is in abdominal or mesenteric lymph nodes, where metastatic disease can be recognized by seeing that there is even mild tracer uptake in a normal-appearing node on CT or MRI.

I-123 OR I-131 METAIODOBENZYLGUANIDINE

Metaiodobenzylguanidine (MIBG) is a norepinephrine analog that is actively concentrated in neuroendocrine tumor cells via the type 1 uptake mechanism. In most NET tumor cells, this molecule is then stored in neurosecretory granules. Originally, MIBG was labeled with I-131 for imaging, and subsequently therapy of pheochromocytoma. Over time its utility has been expanded to other NETs. The imaging properties of I-123 are notably superior to I-131, and clinical comparison studies make it clear that I-123 MIBG should be used in place of I-131 MIBG for imaging.[11] Perhaps most importantly, the use of I-123 makes it possible to obtain high-quality SPECT images, which significantly improves sensitivity. When combined with CT as SPECT/CT, specificity is improved as well.[12,13] In one study, for example, an additional 8% of lesions were conspicuous on I-123 MIBG images compared with I-131 MIBG in patients with pheochromocytoma.[11] **Fig. 1** shows an example of a patient with pheochromocytoma imaged with SPECT/CT using I-123 MIBG.

The normal organ pattern of MIBG distribution includes salivary glands, liver, bladder, and faint uptake in kidneys. The heart also may show substantial uptake of MIBG. The thyroid gland is generally not seen if patients have been adequately prepared with SSKI or Lugols solution to block free I-123 or I-131 uptake in this organ. Brown fat accumulates MIBG as well and is particularly notable in the winter and more common in children. While the base of the neck and mediastinum are perhaps the most common sites for brown fat, other locations include perirenal and perispinal regions.[14] An often overlooked cause for false-positive findings with MIBG is physiologic contralateral adrenal hypertrophy following adrenalectomy.[15]

MIBG uptake in tumor cells may be inhibited by certain medications, including sympathomimetics such as pseudoephedrine, or other drugs including reserpine, calcium channel blockers, tricyclic antidepressants, and labetalol.[16] It is generally

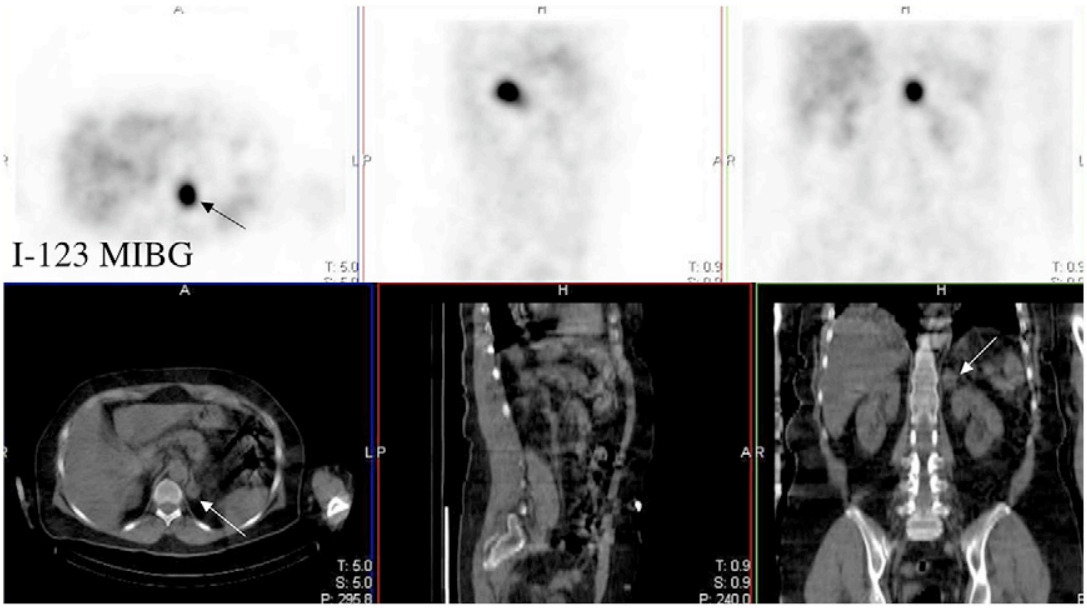

Fig. 1. Single-photon emission computed tomography/computed tomography (CT) examination with I-123 metaiodobenzylguanidine (MIBG) from a patient with a left adrenal pheochromocytoma. Tumor is depicted by white arrows on CT and black arrow on MIBG images.

advised that patients should discontinue these medications 3 to 4 days before administration of MIBG if clinically feasible.

Finally, NETs of the pancreas are not often MIBG positive; therefore there is probably no role for this agent in patients who have these tumor types.[17]

IN-111 PENTETREOTIDE (OCTRE OSCAN)

Somatostatin (SST) is a 28 amino acid peptide that has a variety of endocrine regulatory functions mediated through binding of this peptide to specific receptors on target cells throughout the body. There are five known SST receptor subtypes. Octreotide is an 8 amino acid cyclic peptide derivative of SST that binds primarily to SST receptor types 2 and 5. In-111 linked by a chelating agent to this peptide is marketed under the trade name Octreoscan (In-111 pentetreotide).

Most NETs express SST receptors, predominately type 2. Scintigraphic imaging with In-111 pentetreotide has become one of the standard methods for detection of NETs. Both sensitivity and specificity are improved with SPECT/CT when imaging with In-111 pentetreotide.[18] Imaging at 4 hours helps to avoid interfering with bowel uptake that is typically present at 24 hours. However, at 24 hours after injection the target (tumor)-to-background signal ratio is usually optimal. In patients on chronic therapy, it is advisable to withdraw cold octreotide immediate-release formulation 24 hours before scintigraphy. In patients treated with long-acting formulations, SRS imaging should be performed just before the next long-acting formulation administration.[19]

The normal pattern with In-111 pentetreotide includes intense activity in bladder, kidneys, and spleen, with lesser concentration in normal liver and bowel. Other less common sites of physiologic uptake include gallbladder, thyroid, and rarely pituitary. It is important for clinicians to keep in mind that certain inflammatory lesions will also concentrate this radiopharmaceutical. This is due to the fact that activated lymphocytes express SST receptors. Additionally, other types of malignancies may express these cell surface receptors, including some of the lymphomas.[20]

PET/CT

A number of PET radiopharmaceuticals have been studied as agents for detection of NETs. This section will focus on three in particular: fluorodeoxyglucose (F-18 FDG), which is widely available; Ga-68 octreotide, and F-18 fluorodehydroxyphenylalanine (DOPA). Nearly all modern health care facilities have access to PET or preferably PET/CT. PET has several advantages over imaging methods that use gamma-emitting radiopharmaceuticals such as In-111 pentetreotide or I-123 MIBG, including improved spatial and contrast resolution.

FDG

F-18FDG is an analog of glucose labeled with the positron emitting radioisotope fluorine-18, well known for its use with PET in many types of malignancy. Highly metabolic tumors, reflected by high FDG signal on PET images, tend to be more clinically aggressive. In general, this is true for NETs also. Very often when NETs exhibit strong affinity for FDG, the corresponding level of In-111 pentetreotide uptake or Ga-68 DOTATOC is low or absent, and conversely, when uptake is high with a radiolabeled SST analog, FDG activity in the tumor is low or absent.[21–24]

DOPA AND DOPAMINE

F-18DOPA, originally developed to image the dopaminergic system in the brain, has taken on a new role as a PET imaging agent for detection of neuroendocrine tumors. DOPA represents an intermediary molecule in the synthesis of norepinephrine and other chetacholamines. F-18DOPA is concentrated by neuroendocrine tumors through an amino acid transport system that is upregulated and highly active in the cells of these tumors. Metabolites of this tracer then are trapped in intracellular storage vesicles. Normal image patterns with this agent include high uptake in kidneys and urinary collecting systems. Preparation of patients with Carbidopa before imaging will increase tumor-to-background ratios.[25] Dopamine can similarly be labeled and imaged with F-18. PET/CT imaging using F-18DOPA or F-18 dopamine appears to have a very high sensitivity and specificity for carcinoid tumors and pheochromocytoma while being somewhat less sensitive for detection of pancreatic NETs.[26–31]

GA-68 DOTATOC/TATE/NOC

Ga-68 is a positron emitter that can be tightly labeled to the octreopeptide/chelator complex known as DOTATOC. Ga-68 DOTATOC has notably greater binding affinity for SST receptor 2 than does In-111 pentetreotide.[5] In addition, further small modifications to the octreopeptide molecule yield the other important SST receptor analogs DOTATATE and DOTANOC. DOTATATE has a modestly greater binding affinity for SST receptor 2 than does DOTATOC. The level of affinity for SST receptor 2 is summarized as: DOTATATE>DOTATOC>DOTANOC, and all demonstrate affinity greater than In-111 pentetreotide. DOTANOC has the advantage of better SST receptor 3 and 5 affinity than DOTATOC, DOTATATE, or In-111 pentetreotide.[5]

Several have confirmed the expected improved accuracy of Ga-68 DOTATOC PET/CT compared with SPECT or SPECT/CT imaging with In-111 pentetreotide in patients with NETs.[32–34]

IMAGING CARCINOID TUMORS

The most common among the neuroendocrine tumors, carcinoids have been detected with relatively high sensitivity and specificity for nearly 20 years using In-111

pentetreotide.[35] Modern SPECT imaging with this radiopharmaceutical yields sensitivities in excess of 80% for carcinoid tumor metastases.[36] For detection of radiologically occult primary tumors, the sensitivity is probably somewhat less. In-111 pentetreotide tumor uptake is useful to predict prognosis in patients with disseminated disease. In a large series of patients with metastatic well-differentiated endocrine carcinomas, lack of In-111 pentetreotide tumor uptake was associated with a significantly poorer overall survival.[37] In general, specificity is excellent, particularly when SPECT/CT is used. False-positive results are most commonly observed in inflammatory or infectious lesions and uncommonly in other tumor types.[20] **Fig. 2** shows an example of SPECT/CT with In-111 pentetreotide in a patient with lung carcinoid tumor.

Although sensitivity for detecting carcinoid tumors is notably less with MIBG (on the order of 50% to 60%) compared with In-111 pentetreotide, this radiopharmaceutical may still play a role in the care of some patients with carcinoid tumors.[38] It has become clear that there is a small fraction of patients with tumors that are MIBG-positive and In-111 pentetreotide-negative.[39] Importantly, in one series of 92 metastatic carcinoid patients, nearly 50% had at least one tumor site that was positive with MIBG and negative with In-111 pentetreotide and vice versa.[40] The highest sensitivity with I-123 MIBG generally is seen in the midgut carcinoid tumor subgroup.[41] In patients with advanced stage carcinoid tumors who have negative, or weakly positive, In-111 pentetreotide results, MIBG imaging may be used for selection of patients who might benefit from treatment with large doses of I-131 MIBG.[42]

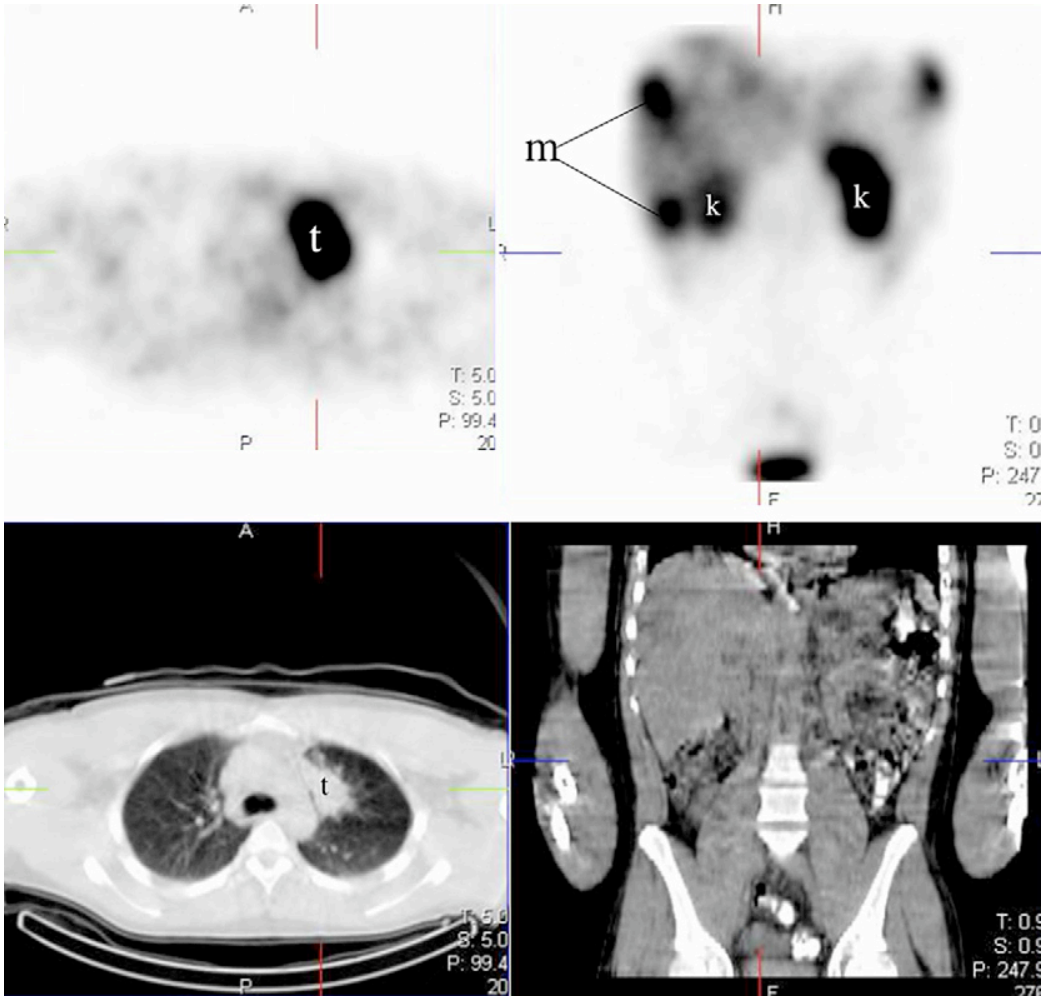

Fig. 2. SPECT/CT Octreoscan images from a patient with primary pulmonary carcinoid tumor metastatic to the liver. Note the liver metastases are not discernible on the noncontrast CT. k, kidneys; m, liver metastases; t, lung carcinoid tumor.

Poorly differentiated carcinoid tumors often do not concentrate either pentetreotide or MIBG in amounts adequate for detection. For these tumors, F-18FDG PET imaging is very likely to be positive.[22–24] **Fig. 3** demonstrates this imaging pattern. The likelihood of FDG tumor positivity on PET images is to some degree related to the ki-67 tumor proliferation index. In one study where octreopeptide imaging was accomplished with Ga-68 DOTATATE and compared with FDG PET findings, the authors found high FDG uptake and low Ga-68 DOTATATE uptake in NET tumors with high Ki-67, whereas they demonstrated low FDG uptake and high DOTATATE uptake in lesions with low ki67 results.[24]

FDG PET/CT in patients with NET, and specifically carcinoid tumors, has the ability to predict patient prognosis. In a study of 98 patients with NETs, 45 of which were intestinal carcinoid tumors, tumor affinity for FDG was strongly associated with poor outcome independent of the results of the Ki67 index.[43] In this study, progression-free survival was dramatically shorter for patients with FDG-positive versus FDG-negative tumors.

PET/CT imaging using F-18DOPA has a high sensitivity and specificity for detection of carcinoid tumors relative to other imaging techniques.[28,29] A large series of patients with carcinoid tumors found a sensitivity for PET DOPA of 96% on a per lesion basis.[26] Further work with this radiopharmaceutical has demonstrated substantial impact on patient management in carcinoid patients, particularly those with occult tumors.[27] In another study, 18F-DOPA PET alone detected more tumor sites than the combination of CT and SPECT octreotide imaging together.[30] In a smaller study, primary tumors were detected by F-18 DOPA in 13 patients (11 had carcinoid tumors), and these tumors were not conspicuous with In-111 pentetreotide or CT/MRI.[31]

Results from Ga-68 labeled octreopeptides imaged with PET also indicate a very high overall sensitivity and specificity for neuroendocrine tumors.[32,44] Ga-68 DOTATOC PET shows a significantly higher tumor detection rate than conventional SST receptor scintigraphy or diagnostic CT in patients with carcinoid tumors. In one comparison study of 84 patients, tumor sensitivity using Ga-68 DOTATOC was found to be 97%, which was significantly higher than either stand-alone CT or SPECT with In-111 pentetreotide.[32] In another comparison study, G-68 DOTATOC-PET was more sensitive in all locations of the body relative to In-111 pentetreotide SPECT except for the liver, where the two methods were found to be essentially equivalent.[33]

Overall, the management of carcinoid patients appears to be improved using PET with Ga-68 octreopeptides. In 64 patients with NET, predominately carcinoid, Ga-68 DTATOC PET/CT changed management in 38% of subjects. The authors noted that the CT component was important, as there were a significant number of lesions

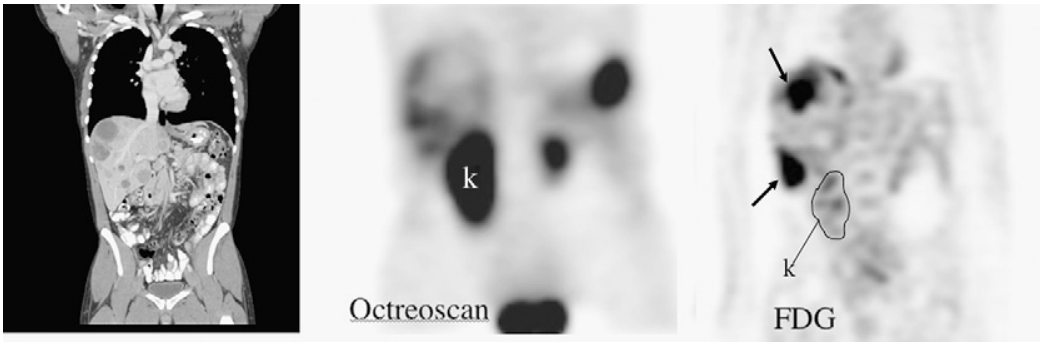

Fig. 3. Example of a patient with dedifferentiated carcinoid tumor liver metastases depicted on CT that do not concentrate, or minimally concentrate, in In -111 pentetreotide. In contrast, these tumors are strongly fluorodeoxyglucose avid on positron emission tomography (*arrows*). k, kidney.

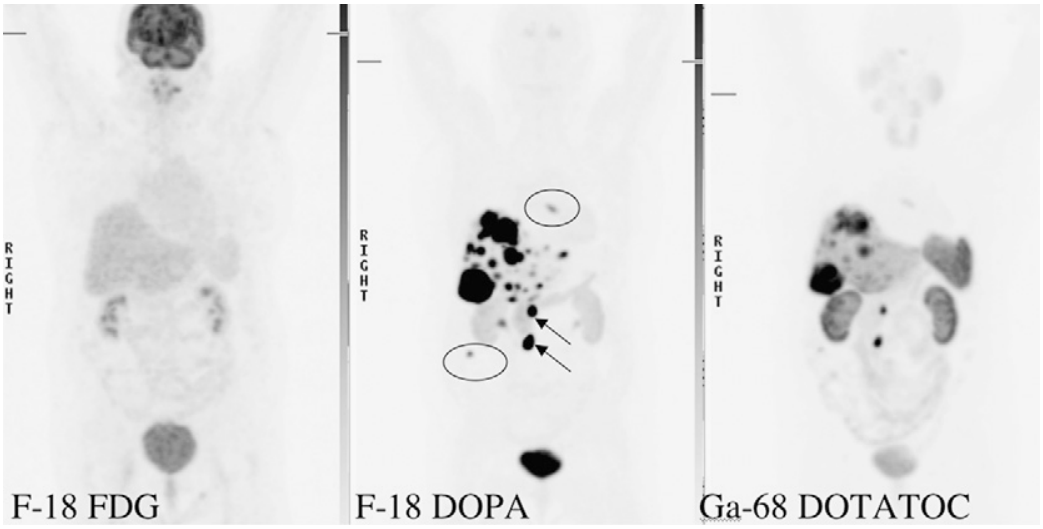

Fig. 4. 55 year-old man s/p hemicolectomy for colon carcinoid. From left to right, volume rendered PET images of F-18 FDG , F-18 fluorodehydroxyphenylalanine (DOPA), and Ga-68 DOTATOC. The FDG study does not demonstrate tumor activity. In contrast both DOPA and DOTATOC are for the most part strongly positive in liver metastases, peripancreatic nodal metastases (*arrows* on DOPA images) mediastinal lymph node (*upper oval*) and mesenteric node (*lower oval*). In this case, however, DOPA images clearly demonstrate stronger signal from almost all tumor sites compared with DOTATOC. Note mild normal pancreatic activity seen on DOPA image.

seen on CT that were not conspicuous on Ga-68 DOTATOC images.[34] Importantly, in this study CT was performed using triple-phase contrast-enhanced imaging. Similar findings relating to improved management of patients with carcinoid tumors also have been reported for other Ga-68 labeled octreotide agents imaged with PET.[45] PET images from three different radiopharmaceuticals are shown in a patient with metastatic carcinoid in **Fig. 4**.

CT and MRI play important roles in evaluating patients with carcinoid tumors. MRI in particular is highly sensitive for detecting carcinoid bone marrow metastases, with a sensitivity approaching 100% in one study.[46] Primary ileal tumors are often seen on CT as small stellate or spiculated masses. CT images may show mesenteric fibrosis near the tumor related to the release of serotonin or other bioactive amines.[47] In many cases, the tumor will be seen containing areas of calcification on CT.[48]

SUMMARY

In summary, functional imaging methods should be combined with CT or MRI to obtain maximal information in patients with NETs. PET/CT is the superior methodology for staging and detection of primary tumors of undetermined location. SPECT imaging (and preferably SPECT/CT) with In-111 pentetreotide or I-123 MIBG will likely be replaced in the coming years by PET/CT with Ga-68 labeled octreopeptides and either F-18 DOPA or F-18 dopamine. Likewise, MIBG imaging will at some point probably be performed with PET/CT using the positron emitter I-124 MIBG. Finally, octreopeptide and MIBG imaging will continue to also play important roles in establishing eligibility for therapy with either Y-90 or Lu-177 labeled DOTA octreopeptides or I-131 MIBG.

REFERENCES

1. Zuetenhorst JM, Taal BG. Metastatic carcinoid tumors: a clinical review. Oncologist 2005;10(2):123–31.

2. Koopmans KP, Neels ON, Kema IP, et al. Molecular imaging in neuroendocrine tumors: molecular uptake mechanisms and clinical results. Crit Rev Oncol Hematol 2009;71(3):199–213.
3. Bombardieri E, Coliva A, Maccauro M, et al. Imaging of neuroendocrine tumours with gamma-emitting radiopharmaceuticals. Q J Nucl Med Mol Imaging 2010; 54(1):3–15.
4. Scarsbrook AF, Ganeshan A, Statham J, et al. Anatomic and functional imaging of metastatic carcinoid tumors. Radiographics 2007;27(2):455–77.
5. Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. Semin Nucl Med 2006;36(3):228–47.
6. Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). Best Pract Res Clin Endocrinol Metab 2007;21(1):43–68.
7. Paulson EK, McDermott VG, Keogan MT, et al. Carcinoid metastases to the liver: role of triple-phase helical CT. Radiology 1998;206(1):143–50.
8. Bader TR, Semelka RC, Chiu VC, et al. MRI of carcinoid tumors: spectrum of appearances in the gastrointestinal tract and liver. J Magn Reson Imaging 2001;14:261–9.
9. Tamm EP, Kim EE, Ng CS. Imaging of neuroendocrine tumors. Hematol Oncol Clin North Am 2007;21(3):409–32.
10. Amthauer H, Denecke T, Rohlfing T, et al. Value of image fusion using single photon emission computed tomography with integrated low-dose computed tomography in comparison with retrospective voxel-based method in neuroendocrine tumors. Eur Radiol 2005;15(7):1456–62.
11. Furata N, Kiyota H, Yoshigoe F, et al. Diagnosis of pheochromocytoma using [123I]-compared with [131I]-metaiodobenzylguanidine scintigraphy. Int J Urol 1999;6(3):119–24.
12. Meyer-Rochow GY, Schembri GP, Benn DE, et al. The utility of metaiodobenzylguanidine single photon emission computed tomography/computed tomography (MIBG SPECT/CT) for the diagnosis of pheochromocytoma. Ann Surg Oncol 2010;17(2):392–400.
13. Rozovsky K, Koplewitz BZ, Krausz Y, et al. Added value of SPECT/CT for correlation of MIBG scintigraphy and diagnostic CT in neuroblastoma and pheochromocytoma. AJR Am J Roentgenol 2008;190(4):1085–90.
14. Okuyama C, Ushijima Y, Kubota T, et al. 123I-metaiodobenzylguanidine uptake in the nape of the neck of children: likely visualization of brown adipose tissue. J Nucl Med 2003;44(9):1421–5.
15. Boersma HH, Wensing JW, Kho TL, et al. Transient enhanced uptake of 123I-metaiodobenzylguanidine in the contralateral adrenal region after resection of an adrenal pheochromocytoma. N Engl J Med 2000;342(19):1450–1.
16. Khafagi FA, Shapiro B, Fig LM, et al. Labetalol reduces iodine-131 MIBG uptake by pheochromocytoma and normal tissues. J Nucl Med 1989;30(4):481–9.
17. Kaltsas G, Korbonits M, Heintz E, et al. Comparison of somatostatin analog and metaiodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. J Clin Endocrinol Metab 2001;86(2): 895–902.
18. Oberg K, Eriksson B. Nuclear medicine in the detection, staging, and treatment of gastrointestinal carcinoid tumors. Best Pract Res Clin Endocrinol Metab 2005; 19(2):265–76.
19. Oberg K, Kvols L, Caplin M, et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004;15(6):966–73.

20. Bushnell DL, Menda Y, Madsen MT, et al. ^{99m}Tc Depreotide tumour uptake in patients with non-Hodgkin's lymphoma. Nucl Med Commun 2004;25(8):839–43.
21. Kayani I, Conry BG, Groves AM, et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. J Nucl Med 2009; 50(12):1927–32.
22. Intenzo CM, Jabbour S, Lin HC, et al. Scintigraphic imaging of body neuroendocrine tumors. Radiographics 2007;27(5):1355–69.
23. Menda Y, O'Dorisio T, Floresca J, et al. Detection of primary and recurrent carcinoid tumors with F-18-FDG PET: comparison with In-111-pentetreotide. J Nucl Med 2003;44:72P.
24. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-Dphe1, Tyr3-octreotate) and 18F-FDG. Cancer 2008;112(11):2447–55.
25. Imani F, Agopian VG, Auerbach MS, et al. 18F-FDOPA PET and PET/CT accurately localize pheochromocytomas. J Nucl Med 2009;50(4):513–9.
26. Koopmans KP, de Vries EG, Kema IP, et al. Staging of carcinoid tumors with 18F-DOPA PET: a prospective, diagnostic accuracy study. Lancet Oncol 2006; 7(9):728–34.
27. Montravers F, Kerrou K, Nataf V, et al. Impact of fluorohydroxy-phenylalanine-18F positron emission tomography on management of adult patients with documented or occult digestive endocrine tumors. J Clin Endocrinol Metab 2009; 94(4):1295–301.
28. Hoegerle S, Altehoefer C, Ghanem N, et al. Whole-body 18F DOPA PET for detection of gastrointestinal carcinoid tumors. Radiology 2001;220(2):373–80.
29. Becherer A, Szabó M, Karanikas G, et al. Imaging of advanced neuroendocrine tumors with (18)F-FDOPA PET. J Nucl Med 2004;45(7):1161–7.
30. Koopmans KP, Neels OC, Kema IP, et al. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. J Clin Oncol 2008;26(9): 1489–95.
31. Ambrosini V, Tomassetti P, Rubello D, et al. Role of 18F-dopa PET/CT imaging in the management of patients with 111In-pentetreotide negative GEP tumours. Nucl Med Commun 2007;28(6):473–7.
32. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 2007;48(4):508–18.
33. Buchmann I, Henze M, Engelbrecht S, et al. Comparison of 68Ga- DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2007;34(10):1617–26.
34. Ruf J, Hueck F, Schiefer J, et al. Impact of multiphase 68Ga-DOTATOC- PET/CT on therapy management in patients with neuroendocrine tumors. Neuroendocrinology 2010;91(1):101–9.
35. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]-and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med 1993;20(8):716–31.
36. Kaltsas G, Rockall A, Papadogias D, et al. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. Eur J Endocrinol 2004;151(1):15–27.
37. Asnacios A, Courbon F, Rochaix P, et al. Indium-111-pentetreotide scintigraphy and somatostatin receptor subtype 2 expression: new prognostic factors for malignant well-differentiated endocrine tumors. J Clin Oncol 2008;26(6):963–70.

38. Binderup T, Knigge U, Loft A, et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J Nucl Med 2010;51(5):704–12.
39. Taal BG, Hoefnagel CA, Valdés Olmos RA, et al. Combined diagnostic imaging with 131I-metaiodobenzylguanidine and 111In-pentetreotide in carcinoid tumours. Eur J Cancer Am 1996;32(11):1924–32.
40. Quigley AM, Buscombe JR, Gopinath G, et al. In-vivo characterization of the functional aspects of carcinoid tumors by imaging somatostatin receptors and amine uptake. J Nucl Med 2003;44(Suppl 5):74p.
41. Ezziddin S, Logvinski T, Yong-Hing C, et al. Factors predicting tracer uptake in somatostatin receptor and MIBG scintigraphy of metastatic gastroenteropancreatic neuroendocrine tumors. J Nucl Med 2006;47(2):223–33.
42. Safford SD, Coleman RE, Gockerman JP, et al. Iodine-131 metaiodobenzylguanidine treatment for metastatic carcinoid. Results in 98 patients. Cancer 2004; 101(9):1987–93.
43. 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(3):978–85.
44. 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 neuroendocrine tumors. Eur J Nucl Med Mol Imaging 2008;35(8):1431–8.
45. Ambrosini V, Campana D, Bodei L, et al. 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. J Nucl Med 2010;51(5):669–73.
46. Meijerj WG, van der Veer E, Jager PL, et al. Bone metastases in carcinoid tumors: clinical features, imaging characteristics, and markers of bone metabolism. J Nucl Med 2003;44(2):184–91.
47. Horton KM, Kamel I, Hofrmann L, et al. Carcinoid tumors of the small bowel: a multitechnique imaging approach. AJR Am J Roentgenol 2004;182(3):559–67.
48. Pantongrag-Brown L, Buetow PC, Carr NJ, et al. Calcification and fibrosis in mesenteric carcinoid tumor: CT findings and pathologic correlation. AJR Am J Roentgenol 1995;164(2):387–91.