Molecular Imaging of Neuroendocrine Tumors

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Neuroendocrine tumors (NET) are a heterogeneous group of tumors that arise from neuroendocrine cells. These tumors may arise from various organs, including lung, thymus, thyroid, stomach, duodenum, small bowel, large bowel, appendix, pancreas, adrenal, and skin. Most are well differentiated and have the ability to produce biogenic amines and various hormones. NET usually occur sporadically but they also be associated with various familial syndromes. For the vast majority of NET, surgical resection is the treatment of choice whenever feasible. Localization of NET prior to surgery and for staging and follow-up relies on both anatomic and functional imaging modalities. In fact, the unique secretory characteristics of these tumors lend themselves to imaging by molecular imaging modalities, which can target specific metabolic pathways or receptors. Neuroendocrine cells have a variety of such target receptors and pathways for which radiopharmaceuticals have been developed, including [¹²³I]/[¹³¹I]-metaiodobenzylguanidine (MIBG), [¹¹¹In]pentetreotide, [⁶⁸Ga] somatostatin analogs, [¹⁸F] fluorodeoxyglucose (FDG), [¹¹C]/[¹⁸F] dihydroxyphenylalanine (DOPA), [¹¹C] 5-hydroxytryptophan (5-HTP) ^{99m}Tc pentavalent dimer-captosuccinic acid ([^{99m}Tc] (V) DMSA, and [¹⁸F] fluorodopamine (FDA). Here, we review the molecular imaging approaches for NET using various radiopharmaceuticals.

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Neuroendocrine tumors (NET) are a heterogeneous group of tumors that arise from neuroendocrine cells. Many of these tumors have secretory capacity and produce biogenic amines and polypeptide hormones—these have been called APUDomas (amine precursor uptake and decarboxylation).¹ NET can be classified by embryonic origin as tumors of the foregut (stomach, duodenum, pancreas, lung, and thymus), midgut (distal jejunum to proximal transverse colon), and hindgut (distal transverse colon to rectum). They are also categorized by the organ of origin as NET of lung, thymus, thyroid, stomach, duodenum, small bowel, large bowel, appendix, pancreas, adrenal, or skin. In the past, many of these tumors were called carcinoids, because they were slow-growing and were thought to be benign. In 2000, recognizing the heterogeneity of presentation, prognosis, and outcome, the World Health Organization (WHO) developed a classification system for NET

reflecting a better understanding of cell biology, therapeutic implications, and pathology.² Three types of NET were defined: (1) well-differentiated neuroendocrine tumor (benign behavior, low grade), (2) well-differentiated neuroendocrine carcinoma (low grade malignant), and (3) poorly differentiated neuroendocrine carcinoma (high grade malignant). Because this classification is relatively new and has not been accepted by all practitioners, varied terminology will be used when referring to the different NET in this review. The goal of this review is to focus on the functional imaging of NET.

RADIOPHARMACEUTICAL IMAGING AGENTS

Localization of NET relies on conventional anatomic imaging modalities (CIM) such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) for staging and follow-up. In addition, molecular imaging modalities using radiopharmaceuticals targeting metabolic pathways and receptors are used extensively. A brief review of the more common radiopharmaceuticals including mechanism of localization follows.

Metaiodobenzylguanidine

Metaiodobenzylguanidine (MIBG) is a structural analog of guanethidine and shares structural features with norepinephrine.³ MIBG is internalized via the norepinephrine transporter and moves into secretory gran-

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ules via vesicular monoamine transporters.⁴ For imaging of NET, MIBG has been labeled with iodine 131/iodine 123. The superiority of ¹²³I over ¹³¹I MIBG has been demonstrated.⁵ Suggested imaging guidelines have been published.⁶

Somatostatin Receptor Scintigraphy

Somatostatin is a small regulatory peptide that functions as a neurotransmitter and has inhibitory and antiproliferative effects. It binds to somatostatin receptors, with several subclasses identified: SSTR1, 2a, 2b, 3, 4, and 5.⁷ The commercially available somatostatin analog, pentetreotide, is labeled with indium 111 and is known as pentetreotide. While most clinicians withdraw treatment with somatostatin analogs prior to somatostatin receptor scintigraphy (SRS) because of concerns over competitive inhibition, others have questioned the need for this.⁸

Although not commercially approved in the United States or Europe, gallium 68 somatostatin analogs, DOTATOC,^{9,10} DOTATATE,^{11,12} and DOTANOC¹³ are being used for positron emission tomography (PET) imaging with promising results. These peptides have stronger chelators and higher affinity binding to tumor than [¹¹¹In]-pentetreotide,¹⁴ and ⁶⁸Ga has superior physical properties compared to ¹¹¹In. It also does not require a cyclotron and can be obtained from a generator, allowing great flexibility.¹⁵ Typical imaging starts approximately 1 hour after injection and is finished on the same day, in contrast to pentetreotide, which is often imaged at 4 and 24 hours.

Dihydroxyphenylalanine

Dihydroxyphenylalanine (DOPA) is an amino acid that is internalized by the LAT2 amino acid transporter and then follows the DOPA metabolic pathway. Carbon Labeling with carbon 11, which has a 20-minute half-life requires a cyclotron on-site. In contrast, fluorine 18 has a half-life of 110 minutes and can be produced off-site. FDOPA is commercially available in Europe but not in the United States. Typically, patients are fasted 4 to 12 hours prior to injection and scanned 30 to 90 minutes after injection.^{16–18} In many centers, patients are pretreated with carbidopa to decrease peripheral breakdown.

5-Hydroxytryptophan

[¹¹C] 5-hydroxytryptophan (5-HTP) is an amino acid developed as a precursor for the serotonin pathway that is present in many NET. This agent is internalized via LAT amino acid transporters and undergoes decarboxylation, similar to DOPA/FDOPA. Currently, 5-HTP is not commercially available and it is only used in few centers. Subjects are fasted approximately 2 to 4 hours prior to injection, pretreated with carbidopa, and scanned within 20 to 35 minutes of injection.^{19,20}

Fluorodeoxyglucose

[¹⁸F] fluorodeoxyglucose (FDG) is an analog of glucose, and thus is a surrogate marker for glucose metabolism. FDG enters the cell through GLUT transporters and is phosphorylated by hexokinase and trapped. The uptake of FDG in NET has been related to GLUT 1 concentration and tumor differentiation.²¹ Procedure guidelines describing the technical aspects of FDG imaging have been reported.²²

Fluorodopamine

[¹⁸F] fluorodopamine (FDA) is an analog of dopamine used as an investigational agent for imaging of paraganglioma at the National Institutes of Health (NIH).²³ The mechanism of action is similar to that of MIBG, with binding to norepinephrine transporter followed by internalization and subsequent handling along the same path as DOPA. Advantages of FDA over MIBG include being a PET reagent and completion of imaging the same day. Patients are fasted overnight and imaged is starting approximately 10 minutes following injection.^{23–25}

Technetium 99m (V) DMSA

Technetium 99m (V) DMSA is an agent that resembles the phosphate molecule.²⁶ The mechanism of localization is thought to localize via phosphate metabolism, with uptake by inorganic phosphate transporters.²⁷ This radiopharmaceutical has been used with variable success in patients with medullary thyroid carcinoma (MTC).

GASTROENTEROPANCREATIC TUMORS

Gastroenteropancreatic (GEP) tumors constitute a heterogeneous group of NET of the stomach, pancreas, and bowel. Much of the literature concerning functional imaging of GEP groups together diverse tumor types. Surgical resection is the primary treatment of GEP, even in patients with metastatic disease, in whom debulking may significantly improve quality of life, survival, and performance status.²⁸ Imaging plays an important role in evaluation of extent of disease at presentation and during follow-up.

Overall, the results with radiolabeled MIBG in GEP are variable (Table 1) and not as favorable as those in patients with pheochromocytoma. The varying sensitivity may be related to tumor subtypes; for example, carcinoid patients with high serum levels of serotonin are more likely to be positive on ¹³¹I-MIBG (80%) than those with low serotonin (12%).²⁹ In a study comparing MIBG and SRS in 57 patients with metastatic GEP, SRS was superior to MIBG, especially in high-grade tumors and pancreatic NET, with an overall sensitivity of SRS of 91.2% compared to 49.1% for MIBG.³⁰ For SRS, no significant differences were seen between pancreatic

Table 1. Sensitivity for Detection of Gastroenteropancreatic Tumors

Reference	Patient-Based Sensitivity (lesion-based sensitivity in parentheses)							
	No. of Patients ^a	MIBG	SRS	⁶⁸ Ga Somatostatin Analogs	FDG	FDOPA	CT	MRI
29	43	65% ^j						
157	23	47% ^j	76%					
158	11	36% ^{b,k}	91% ^b					
		18% ^h	36% ^h					
30	57	49% ^l	91%					
36	149		92.3% ^b				80% ^b	
			(92.4%) ^b				(79.4%) ^b	
159	40 ⁱ		91%				91%	
			(89.6%)				(72.6%)	
37	160		78%				71% ^d	
160	145		100% ^c					
49	14 ^f		86%				36%	50%
161	64		82% ^b				(95%) ^b	(98%) ^b
			(49%) ^b				(79%) ^b	(95%) ^b
70	35 VHL only		59%					
162	101		94%				66%	79%
163	60		67% ^b				94% ^b	
			77% ^h				94% ^h	
164	13		0% ^e			100%		
16	17		71%		59%	65%	76%	
			(57%)		(29%)	(65%)	(73%) ^d	
40	33		78%			63%		
165	43		86% ^g			96% ^g	96% ^g	
			78% ^h			89% ^h	87% ^h	
166	7		71%		43%			
43	13		90%		54%		69%	
10	72		52%	97% DOTATOC	92%		61%	
167	15			100% DOTATOC	60%			
11	17			82% DOTATATE	66%			
12	14			100% DOTATATE		57%		
38	11			100% DOTATNOC		64%		

^aData for GEP only; some series include small numbers of unknown primary or other primaries.

^bSensitivity for liver involvement.

^cSensitivity for bone involvement.

^dCIM (anatomical imaging typically MRI and CT).

^eAll patients had negative SRS as inclusion criteria.

^fInsulinoma.

^gSensitivity for carcinoids.

^hSensitivity for primary tumor.

ⁱNonfunctional tumors.

^jIodine 131-MIBG.

^kIodine 123-MIBG.

^lIodine 123- or 131-MIBG.

versus non-pancreatic tumors (91.3% *v* 90.9%), but for MIBG, sensitivity for pancreatic NET (9.1%) was significantly lower than that for non-pancreatic NET (58.7%). For high- versus low-grade tumors, SRS had sensitivities of 57.1% and 96%, respectively, whereas for MIBG, the sensitivities were 0% and 56%, respectively. Others have reported similar results.^{31,32}

Studies of SRS almost invariably show a high sensitivity for GEP (Table 1) except for insulinoma (see below), which appears to have a much lower detection rate.^{33–35} Sensitivity for metastatic gastrinoma, carcinoid, and other GEP is often greater than 80% and up to 94%. Sensitivity for metastatic disease tends to be higher than for primary tumors, and in

many studies, SRS detects lesions not seen with anatomic imaging.^{36,37}

Encouraging results have been observed with ⁶⁸Ga somatostatin analogs.^{9–13} High sensitivities for GEP ranging from 82% to 100% have been described. In two series where the analogs had 100% sensitivity, FDOPA only detected 57% to 64%, and had lower per lesion sensitivity and less intense uptake.^{12,38} Several studies have thus concluded that ⁶⁸Ga analogs are superior to FDOPA and should be used first,^{12,38} with FDOPA reserved for somatostatin-negative and serotonin-positive tumors.

The first study using radiolabeled DOPA for imaging NET utilized [¹¹C] DOPA and detected 48% of primary lesions and 73% of metastasis.³⁹ Since then, due to limitations resulting from the short half-life of ¹¹C, much of the work has been done with FDOPA. In two separate reports of patients with gastrointestinal carcinoid, the sensitivity of FDOPA ranged from 93% to 97% with an impact on management in 50% of the patients,^{40,41} whereas in patients with non-carcinoid GEP, the sensitivity was 25%. In contrast, SRS sensitivity was similar for both, with values of 81% and 75%, respectively.

Koopmans et al compared FDOPA, 5-HTP, SRS, and CT in 24 patients with abdominal carcinoid tumors.²⁰ On a patient basis the sensitivity for carcinoid was 100% for 5-HTP, 96% for FDOPA, 96% for CT, and 86% for SRS. FDOPA detected the largest number of lesions (87%) and 78% were found by 5-HTP, whereas SRS only detected 49%. In pancreatic islet cell tumors, FDOPA and SRS detected fewer lesions than 5-HTP. With all modalities, addition of CT improved lesion sensitivity.

Early studies in NET patients recognized that FDG had low sensitivity for these often slow-growing tumors. In a small study by Adams et al, FDG was negative in well-differentiated NET with low Ki-67 antigen expression, whereas it was positive in those with high Ki-67 expression. SRS showed the opposite pattern.⁴² In a study of 16 NET patients, FDG was markedly positive in all eight patients with aggressive NET, identifying metastatic sites in 83%. In contrast, only one of eight non-aggressive NET had weak FDG uptake, and the remainder had none.⁴³

It has been shown that patients with tumors with greater Ki-67 do poorly compared to those with low Ki-67 expression.⁴⁴ The hypothesis that FDG uptake, which is increased with proliferation, may be a useful marker of prognosis was evaluated in 38 NET patients imaged with SRS and FDG.⁴⁵ Overall, FDG was positive in 39% of patients and SRS was positive in 71%. Early progression was seen in 93% of FDG-positive patients and 82% of SRS-negative patients. In contrast, only 9% of FDG-negative patients and 26% of SRS-positive patients had early progression.

A comparison of SRS and FDG in patients with carcinoid found that 86% of primary tumors were localized with SRS, but only 57% with FDG.⁴⁶ Patients with

metastatic disease were positive with SRS in 69% of cases, in 47% with FDG, and in 56% with anatomic imaging. Others have had similar results in tumors with high proliferation comparing SRS to FDG (Figure 1)³² and also with ⁶⁸Ga somatostatin analogs versus FDG. For example, a study of ⁶⁸Ga DOTATATE and FDG in 38 patients with various types of NET, including 28 GEP, showed superior results with the former (82% *v* 66%).¹¹ When stratified by grade, only 6% of high-grade NET localized with ⁶⁸Ga DOTATATE compared to 97% with FDG; in contrast, 97.6% of low-grade lesions localized with DOTATATE compared to 17% with FDG.

Thus, there appears to be good correlation between the classification of NET and the sensitivity of detection with these radiopharmaceuticals. In practice, some have recommended initial imaging with SRS since these are often positive in both malignant and benign tumors, with FDG imaging if SRS is negative.

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (PNET), also called islet cell tumors, are rare. The most common PNET are gastrinomas, insulinomas, and nonfunctioning tumors; less frequent are vasoactive intestinal polypeptide-secreting tumors (VIPomas), glucagonoma, pancreatic polypeptide-secreting tumors (PPomas), somatostatinomas, corticotropin-releasing hormone-secreting tumors (CRHomas), calcitoninoma, adrenocorticotrophic hormone-secreting tumors (ACTHomas), growth hormone releasing factor-secreting tumors (GRFomas). Functional tumors secrete hormones and often present early with classical endocrine features related to the hormone secreted. In contrast, nonfunctional tumors do not produce or secrete hormones and tend to present late with symptoms related to mass, such as pain or obstruction. Due to the low incidence of PNET, most imaging reports are either very small or lump the diverse histologies together.

Insulinomas have an estimated incidence of 4 per 1 million person-years.⁴⁷ Approximately 90% of these tumors are benign and unifocal⁴⁷ and most are less than 2 cm in size. Detection rates with modern CT imaging, or endoscopic and intraoperative US are high, typically greater than 94%.⁴⁸ Surgical exploration by an experienced surgeon in combination with intraoperative US detects most insulinomas. Therefore, the main role of imaging is in excluding metastatic disease in patients with malignant lesions.

SSTR2 and SSTR5 are the two main receptors expressed in approximately 70% of insulinomas.³⁴ Reports show that the sensitivity of SRS reflects the incidence of receptor presence and ranges from 60% to 63%,^{33,34} although one study showed a sensitivity of 87.5% when single-photon emission computed tomography (SPECT) was used.⁴⁹

Widely discrepant results have been reported with

Figure 1. Patient with nonfunctional well-differentiated pancreatic neuroendocrine carcinoma (Ki-67 <1%). Left upper panel shows multiple SRS-positive metastatic liver lesions (thin arrows) and uptake in the tail of the pancreas primary (block arrow). Right upper panel shows FDG images with partial visualization of some of the liver metastasis and nonvisualization of the primary. Lower panel shows contrast CT showing hypervascular liver lesions and the primary in the tail of the pancreas (arrow).

FDOPA in insulinomas. In one series, FDOPA detected nine of 10 lesions, including two focal lesions in patients with islet cell hyperplasia, whereas the sensitivity of CT was 30% and that for MRI, 40%.⁵⁰ In another report, only one of five insulinomas was positive on FDOPA.⁵¹

Gastrinomas are among the most common PNETs. The gastrin these tumors secrete causes the Zollinger-Ellison syndrome (ZES). Some 80% to 90% of gastrinomas are located in the so-called gastrinoma triangle (duodenum, pancreatic head, and hepatoduodenal ligament), with up to 50% arising in the duodenum. Most sporadic gastrinomas present as solitary lesions and over half are malignant. Common sites of spread include local lymph nodes and liver.⁵² These tumors almost invariably express somatostatin receptors, especially SSTR2,⁵³ and SRS sensitivity is high.

In a prospective study, 80 ZES patients were evaluated with US, CT, MRI, angiography, bone scanning, and SRS.⁵⁴ Extrahepatic gastrinomas and liver metastases were identified by US in 19% of patients, by CT in 38%, by MRI in 45%, by angiography in 40%, and by SRS in 70%. SRS was as sensitive as all other tests combined (59%). In 24 patients with metastatic liver disease, the sensitivity for the detection of any liver lesion was 46% for US, 42% for CT, 71% for MRI, 62% for angiography, and 92% for SRS. SRS was significantly better than all of

the conventional imaging methods in the identification of gastrinomas later found at surgery, but still missed 20% of foci. Another study reported SRS detection of 81% of disease sites with visualization of 83% of tumors identified by all other techniques. In 35% of patients, SRS identified additional sites not previously known. For known duodenopancreatic tumors, SRS and endoscopic US (EUS) each localized 67%, and the combination of the two detected 92%.⁵⁵ Others have found that the sensitivity for detecting duodenal primaries is less than that for pancreatic primaries, likely due to their smaller size.⁵⁶ SRS alters patient management in 17% to 47% of cases.⁵⁷⁻⁵⁹

Pancreatic VIPomas are rare, and only a small number have been described in the literature. They usually arise in the pancreas and less frequently, in the duodenum or retroperitoneum. Primary tumors are often large and are usually metastatic at the time of presentation. In a series of 11 patients, SRS was superior to CIM, detecting 91% of primary tumors and 75% of the patients with metastases.⁶⁰ Kaltsas et al described four VIPomas with metastatic disease; none had MIBG uptake, but all had SRS uptake in metastasis, although only one of two pancreatic masses was positive.³¹

Glucagonomas are rare tumors that arise from pancreatic alpha cells. They secrete glucagon, and diabetes and hyperglycemia are common. Glucagonomas usu-

ally present as large pancreatic tumors, often with evidence of metastatic disease, most commonly to the liver.⁶¹ SRS has shown localization in 95% to 100% of primary or metastatic sites.^{61,62} Although most glucagonomas in one series had less than 3% Ki-67 positivity,⁶¹ there is a case report with positive FDG uptake in a primary pancreatic lesion.⁶³

Somatostatinomas are rare tumors of D-cell origin with excessive secretion of somatostatin. These tumors typically originate in the pancreas or duodenum. Due to their rarity, only case reports have documented SRS^{64,65} and FDG uptake.⁶⁶

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal-dominant syndrome associated with a genetic defect in the *MEN1* gene. It is characterized by a variety of endocrine tumors, most commonly involving the parathyroids, endocrine pancreas, pituitary, and duodenum. The most common pancreatic tumors are gastrinomas, insulinomas, and nonfunctioning tumors.⁶⁷ In a report of MEN1 patients with gastrinomas, SRS and EUS revealed the primary tumor in 64%⁶⁸ of patients with negative CIM.

Von Hippel Lindau (VHL) is an autosomal-dominant neoplastic syndrome resulting in benign and malignant tumors and cysts of various organs, with a series of 256 patients reporting a 12% incidence of solid pancreatic lesions.⁶⁹ Larger tumors were associated with hepatic metastases and imaging was recommended in order to intervene when tumors reach 2 to 3 cm to prevent liver metastases.⁶⁹ In a separate series, SRS had 60% sensitivity for detection of these pancreatic tumors,⁷⁰ perhaps related to the limited presence of SSR2A in 47% of patients.

In summary, it is clear that it is useful to know the histological subtypes of GEP in selecting the optimal imaging reagent. Current European Neuroendocrine Tumor Society guidelines indicate that SRS is the most sensitive single screening method for extrahepatic disease and suggest that it may be used after CT or MRI before consideration for surgical resection.⁷¹ These guidelines may require modification as new imaging reagents are evaluated. In GEP, the role of MIBG is limited to selecting candidates for [¹³¹I]-MIBG therapy. Most centers rely on SRS, although the power of PET and the favorable characteristics of the newer ⁶⁸Ga somatostatin analogs make them superior to SRS. Like MIBG, SRS and ⁶⁸Ga somatostatin analogs also will be used to select candidates for lutetium 177 and yttrium 90 somatostatin radiotherapy. FDOPA is also an extremely useful reagent in certain GEP, particularly well-differentiated tumors that produce serotonin. 5-HTP, while useful, is limited by the short half-life of ¹¹C and the need for a cyclotron on-site. Last, FDG will likely be most useful in patients with high grade tumors with high proliferation and in prognostic stratification.

NEUROENDOCRINE TUMORS OF THE LUNG

Neuroendocrine tumors of the lungs are thought to originate from enterochromaffin or Kulchitsky cells and are located in the bronchial mucosa,⁷² although others have suggested an undifferentiated bronchial stem cell origin. Bronchial carcinoids account for <2% to 5% of all lung tumors^{73,74} and represent 25% of all carcinoids. There is a spectrum within neuroendocrine tumors of the lung,⁷⁵ with tumors ranging from well-differentiated, rarely metastatic to more aggressive, poorly differentiated large (LCNEC) and small cell neuroendocrine carcinomas. The majority of these tumors are perihilar and patients present with recurrent pneumonia, hemoptysis, cough, and chest pain, whereas peripheral tumors are usually asymptomatic. Paraneoplastic syndromes from hormonal secretion are more frequent with atypical carcinoids and usually take the form of ectopic Cushing's or carcinoid syndrome. Staging is important as most therapeutic strategies involve surgical resection, if feasible. In the following section, small cell lung carcinoma (SCLC) will not be discussed as it is often considered separately.

Most bronchial carcinoids express SSTR and several reports have evaluated SRS in these tumors. In two small series, 14/14 primary bronchial carcinoids were visualized with SRS.^{76,77} In addition, a sensitivity of 90% and specificity of 83% were observed when both primary and metastatic disease were considered.⁷⁶ In a separate report, SRS detected a primary lung carcinoid in 81% (13 of 16) of patients with the primary in place and in seven of nine pulmonary recurrent/metastatic sites. CT detected 94% and 89%, respectively.⁷⁸ CT detected liver metastases in 14 patients; nine of these were also positive on SRS. In another series following 31 patients with bronchial carcinoid for restaging or follow-up, SRS confirmed findings of other modalities in 71% of patients, found new tumor sites in 19%, and clarified findings in 6%. In 97% of cases SRS found the same as or more lesions than CIM.⁷⁹ Furthermore, SRS imaging had an effect on patient management in 25.8% of patients. Limited work has been performed with ⁶⁸Ga somatostatin analogs in pulmonary NET, and results are promising.^{13,80}

It has been recognized that FDG has low uptake and thus low sensitivity for detecting well-differentiated NET compared to high-grade NET.⁸⁰⁻⁸² Erasmus et al first reported that the majority of typical bronchial carcinoids did not have abnormal increased FDG uptake above mediastinal blood pool and had low SUVmax (a measure of uptake) values <2.5 (mean, 1.9).⁸¹ Others have since shown a correlation between GLUT1 and SUVmax in lung NET and confirmed the poor uptake in well-differentiated tumors.²¹ This is consistent with the low proliferation rates of typical carcinoids (1.7% ± 1.4%) and their poor uptake of FDG.⁸³ Somewhat at odds with these imaging reports was the

study of Daniels et al, who showed a 72.7% detection rate of typical carcinoids with FDG and 80% for atypical carcinoids.⁸⁴ As with other cancers, increased intensity of FDG uptake has been correlated with worse prognosis.⁸² No reports have evaluated the role of FDOPA in lung NET aside from SCLC, in which it proved inferior to FDG.⁸⁵

In summary, benign and well-differentiated lung NET are often negative with FDG, whereas the more aggressive and atypical LCNEC or SCLC tend to be FDG-positive. The converse is true for SRS.

THYMIC NEUROENDOCRINE TUMORS

Primary tumors arising from the thymus derive from thymic epithelial cells (thymoma, thymic carcinoma), lymphocytes (lymphoma), Kulchitsky cells (neuroendocrine tumors), or thymic and fatty tissue (thymolipomas). Thymic tumors may present with mass effect, hormone secretion, or paraneoplastic syndrome. Although functional imaging is useful in thymomas, thymomas are not considered neuroendocrine tumors and will not be discussed further.

Thymic NET (also called thymic carcinoids) are rare.⁸⁶ They have an increased incidence in patients with MEN1. Gibril et al evaluated the utility of SRS for surveillance of thymic carcinoids in MEN1 patients.⁸⁷ In this series, thymic carcinoids occurred in seven of 85 (8%) patients followed for a mean of 8 years. CT and MRI detected all seven lesions, whereas SRS was positive in only four of six. Furthermore, metastatic bone disease of the spine was detected by MRI in two patients but not by SRS. This led the authors to recommend yearly follow-up with CT of the chest for MEN1 patients older than 25 years of age and MRI of the spine as surveillance for bone metastatic disease. In a smaller series of MEN1 patients, all four patients with thymic carcinoids were SRS-positive.⁸⁸ Data evaluating the role of ⁶⁸Ga somatostatin analogs in thymic carcinoid are limited.⁸⁹

Data on other radiopharmaceuticals are also limited. There are several case reports indicating FDG uptake in thymic carcinoids.^{90,91} Note that FDG uptake is frequently seen in thymic hyperplasia, particularly in pediatric patients and younger adults with thymic rebound post-chemotherapy. This uptake is generally uniform and of low intensity, with mean SUVmax of <3.0.⁹² Limited data on MIBG imaging of thymic carcinoids suggest its performance is similar to that reported in other carcinoids.^{93,94} No reports of FDOPA imaging in thymic lesions are available.

In summary, limited data are available in this rare tumor. CT and MRI are often used as primary staging modalities and SRS is the most widely used functional modality. The role of other radiopharmaceuticals is not well defined.

MEDULLARY THYROID CARCINOMA

MTC is a NET that arises from the parafollicular C cells of the thyroid. It accounts for 3% to 10% of all thyroid malignancies.⁹⁵ The majority of these tumors are sporadic, but they can also be associated with MEN2A, MEN2B, and familial MTC. Prognosis is related to tumor size, invasion, grade, and stage at presentation. During initial staging, cervical lymph node metastases are often present and distant metastasis may also be present.⁹⁶ MTC is a surgically managed disease, which is currently the only definitive curative treatment. Once metastatic disease has occurred, conventional treatment modalities such as radiation therapy, chemotherapy, or immunotherapy are typically ineffective.⁹⁷ Initial surgery usually consists of total thyroidectomy with complete central neck and lymph node dissection, and at the time of presentation, functional imaging methods are not generally indicated unless calcitonin (hCT) levels are very high or distant metastases are suspected. After initial surgery the earliest evidence of recurrence and metastatic disease is usually an elevation in hCT and/or carcinoembryonic antigen (CEA) level. Calcitonin levels correlate with tumor burden and size, with levels above 1,000 pg/mL corresponding to tumor with median size >25 mm versus those <1,000 pg/mL being 7 mm.⁹⁸

Surgery is also used to manage metastases, and once elevated tumor markers are detected, imaging is performed to identify sites of disease. Anatomic imaging routinely includes neck US, CT, and/or MRI. US detects 28% to 97% of nodal recurrences and CT identifies 38% to 70%,^{99,100} while MRI localizes 44% to 90%.^{101,102} Because of the limitations and nonspecificity of anatomic imaging, functional imaging is also used.

[^{99m}Tc] (V) DMSA has variable success in MTC. Localization in nine of 10 primary MTC and five of nine metastatic sites has been reported.²⁶ In other studies, the sensitivity for tumor detection has been quite variable and often lower than other radiopharmaceuticals (Table 2). [¹³¹I]/¹²³I]-MIBG also has limited success imaging MTC (Table 2). Currently, MIBG is used mainly to select patients with metastatic disease for [¹³¹I]-MIBG therapy.

The ability of SRS to detect metastatic MTC is also limited. This may be related to low SSTR2, 3, or 5 expression, which in MTC was shown to be present in only 75% of cases.¹⁰³ In patients likely to have recurrent disease based on elevated hCT, reported per-patient sensitivities range from 19% to 72% (Table 2). In particular, lesions less than 1 cm are not effectively detected by SRS.¹⁰⁴ The sensitivity of SRS also correlates with hCT levels.¹⁰⁵ A study using [⁶⁸Ga] DOTATATE reported a per-patient sensitivity of 72%, compared to 78% for FDG.¹⁰⁶ [⁹⁰Y] DOTATOC has also demonstrated antitumor effects in MTC, and in the future, SRS imaging may be used to select candidates for therapy.¹⁰⁷

Table 2. Sensitivity for Detection of Medullary Thyroid Carcinoma

Reference	Patient-Based Sensitivity (lesion-based sensitivity in parentheses)							MRI
	No. of Patients	MIBG	SRS	FDG	FDOPA	DMSA	CT	
168	20	(64%) ^d						
169	9	38% ^d				89%		
105	29	41% ^e	31%	50%				
110	40	8% ^d		95%			72%	66%
170	26		57%					
171	22		71%			58%		
104	18		50%			67%	50%	
109	19		42%	79%			58%	
117	26		19%	50%		21%	40% ^a	40% ^a
115	85		25%	78%		33%	50%	82
106	18		72% ^b	78%				
116	20		71%	73%			61%	
108	28		20%	62%				
100	55			58%				
111	33			76%			74%	85% ^c
112	11		(52%)	(44%)	(63%)		(81%) ^a	(81%) ^a
114	15			47%	47%			
113	26			58%	81%		58%	

^aStudies used either CT or MRI.^bGallium 68 DOTATATE.^cMRI of bone.^dIodine 131-MIBG.^eIodine 123-MIBG.

A number of studies have evaluated the use of FDG in MTC. The sensitivity for tumor detection on a per-patient basis ranges from 47% to 95% (Table 2) and on a per-lesion basis ranges from approximately 40% to 96%, although these are probably overestimates. These large variations are likely related to differences in tumor burdens, manifested by the hCT. As with SRS, the sensitivity of FDG increases with hCT levels.^{100,105,108,109} For example, Ong et al reported that the sensitivity of FDG was 78% when hCT was greater than 1,000 pg/mL compared to 20% for patients with levels less than 1,000 pg/mL, and no tumors were detected in patients with hCT less than 510 pg/mL.¹⁰⁸

In most comparative studies the sensitivity of FDG is significantly higher than that of SRS (Table 2), and is usually better than CIM (mainly CT). An exception is for liver and lung metastases, where CT and MRI are more sensitive.^{100,110} For example, in one series only 56% of liver lesions seen with CT were positive on FDG.¹¹¹

The initial report evaluating FDOPA in patients with MTC showed a sensitivity of 63% on a per-lesion basis, higher than that of FDG (44%) and SRS (52%), whereas CIM detected 81%. CIM also had the highest number of false positives.¹¹² Another report in 26 MTC patients found that FDOPA identified 94% of metastatic deposits

compared to 62% for FDG.¹¹³ Not only was the sensitivity of FDOPA higher than that of FDG, the intensity of uptake was also higher, with mean SUVmax of 20 versus 7 for FDG. In contrast, lower sensitivities were reported in another study where both FDG and FDOPA detected seven of 15 patients with MTC.¹¹⁴ This lower sensitivity was likely related to low tumor burden (mean hCT of 256 pg/mL).

In summary, of the functional methods, it appears that FDOPA and FDG have the highest sensitivities for MTC, and a combination of anatomic and functional methods appears to be most optimal. For example, the combination of FDG PET and MRI increased tumor detection from 68% for FDG alone to 90% with the combination.¹¹⁵ However, in many series, even when a combination of functional and anatomic imaging is used, 22% to approximately 40% of patients with elevated hCT are negative.^{106,116,117}

MERKEL CELL CARCINOMA

Merkel cell carcinoma (MCC) is a rare malignant and highly aggressive skin tumor that arises from neuroendocrine cells within the basal layer of the epidermis, affecting mainly sun-exposed areas. Up to 50% of MCC have lymph node metastasis at presentation or develop

Table 3. Sensitivity and Specificity of FDG for Merkel Cell Carcinoma

Reference	No. of Patients	FDG Sensitivity ^a	FDG Specificity ^a
129	21	(94%)	(100%)
128	11	92%	100%
130	23	79%	96.1%
132	16	(85.7%)	(96.2%)

^aPatient-based values (lesion-based in parentheses).

them during follow-up. Typical sites of metastatic disease include lymph nodes, skin, lung, CNS, and bone.¹¹⁸ Treatment of primary MCC consists of surgical resection for cure or regional control. Given that pre-treatment staging is an independent predictor of survival,¹¹⁹ nodal sampling is frequently performed. Although patients often undergo CT scans for evaluation of extent of disease,¹²⁰ CT has a detection rate of only 20% for nodal disease at initial staging.¹²¹

Reports of functional imaging of MCC are limited. There are a few cases of MIBG use in MCC patients,¹²² and while the experience with SRS is greater, it also is limited.¹²³⁻¹²⁶ The largest series examined 20 patients with MCC using SRS. The sensitivity was 78% and specificity was 96%.¹²⁵ Two smaller reports had per-patient sensitivities of 57% and 80%.^{123,124} While its clinical utility compared to CIM is questionable,¹²⁵ SRS can be used for selection of candidates for ⁹⁰Y/¹⁷⁷Lu somatostatin receptor therapy.¹²⁷

A larger experience has been reported with FDG, which has an overall sensitivity for detecting nodal or metastatic MCC of 79% to 94% and high specificity, greater than 96% (Table 3). This is not surprising in light of the moderate to high Ki-67 index often found in MCC.¹²⁸ The intensity of FDG uptake is generally high, with mean SUVmax values ranging from approximately 4 to 13.6.¹²⁸⁻¹³² Given the high incidence of metastatic disease and its prognostic significance, it appears that FDG has a role in evaluating patients at high risk for metastases. For example, FDG results changed staging in 33% of patients in one study and altered management in 43%.¹²⁹ Last, two preliminary reports of FDOPA in a total of eight MCC patients suggest that FDOPA has poorer contrast and sensitivity than FDG.^{132,133} In summary, FDG is the best functional imaging reagent for assessing metastatic disease in patients with MCC.

PHEOCHROMOCYTOMA/PARAGANGLIOMA

Paragangliomas (PGLs) are rare tumors that originate from chromaffin-producing cells. When they originate in the adrenal gland they are referred to as pheochromocytoma (PHEO), whereas in all other locations they

are referred to as PGLs. These lesions are mostly sporadic but can be hereditary. Differentiation between benign and malignant PGLs cannot be made histologically and requires the presence of metastatic disease to confirm malignancy.¹³⁴ Most PGLs are sympathetic in origin, whereas those originating in the head and neck are most often of parasympathetic origin and generally do not produce catecholamines. For the purposes of this imaging review, head and neck PGL will be discussed separately (see below).

Non-Head and Neck PHEO/PGL

The diagnosis of non-head and neck PHEO/PGL is made biochemically. Imaging is used to localize the primary tumor, evaluate for multicentric disease, and to assess for metastatic disease. Functional imaging also may help confirm a diagnosis when the biochemistry results are borderline. Furthermore, it is important to adequately localize disease prior to intervention. In addition, MIBG and SRS scintigraphy may be used to select candidates for radiolabeled therapy.

[¹³¹I/¹²³I]-MIBG are the prototypical reagents for imaging PHEO/PGL. ¹³¹I has high overall sensitivity, typically greater than 85% (Tables 4 and 5), and results with [¹²³I]-MIBG are superior to those with [¹³¹I]-MIBG.^{5,135} The detection rate is particularly high in benign disease. Overall, the sensitivity of MIBG for metastatic disease appears to be slightly lower than for primary tumors, perhaps related to dedifferentiation or to genetically determined differences in phenotype. The specificity of MIBG is also high, greater than 89% to 100%.^{136,137} Visualization of normal adrenal glands with [¹²³I]-MIBG imaging occurs in 31% to 50% of cases, and can lead to false positive results.^{5,138} Note that uptake in the normal adrenal is typically less than or equal to that in the liver, whereas uptake in PHEO is greater than in the liver in 88% of patients.¹³⁸

Several studies have evaluated the use of SRS in benign PHEO/PGL and found low sensitivity, ranging from 25% to 28.5% (Table 4). In contrast, the sensitivity of SRS for malignant PHEO/PGL is usually high, ranging from 87.5% to 88.9% (Table 5).

The NIH group has reported extensively on the role of FDA PET imaging in PHEO/PGL. The sensitivity of FDA in metastatic PHEO/PGL is high, ranging from 88% to 100% on a per-patient basis or 70% to 97% on a per-lesion basis.^{25,135,139-141} Comparisons have shown higher sensitivity for FDA than MIBG.^{135,140,141}

Shulkin et al were among the first to report on the use of FDG for PHEO/PGL imaging. They observed that it had a per-patient sensitivity of 76% overall, and 58% for benign PHEO/PGL compared to 88% for malignant disease. In patients who were both MIBG- and FDG-positive, MIBG was superior in 56% and equal or better than FDG in 88%.¹⁴² Case reports have described a "flip-flop" phenomenon where MIBG negative lesions

Table 4. Sensitivity for Detection of Benign Pheochromocytoma/Paraganglioma

Reference	No. of Patients ^a	Patient-Based Sensitivity (lesion-based sensitivity in parentheses)						
		MIBG	SRS	FDG	FDA	FDOPA	CT	MRI
136	51	78.4% ^c						
156	48	98% ^d						
137	32	90.6% ^d					90%	93.3%
140	17	87.5% ^d	28.5%		87.5%		100% ^b	100% ^b
172	32		(25%)					
142	12	83% ^e		58%				
25	20	(77%) ^d		(88%)	(77%)	(81%)	(100%) ^b	(100%) ^b
144	17	71% ^d				100%		100%
173	24	(52%) ^c				(85%)	(70%) ^b	(70%) ^b
174	10					90%		
175	22					100%	66%	
139 VHL	7	57% ^e			100%		100	83%
141	26	(78%) ^c			(78%)		(97%)	(92%)

^aData for benign PGL only; some studies included both benign and malignant PGL.

^bStudies used either CT or MRI.

^cIodine 131-MIBG.

^dIodine 123-MIBG.

^eEither ¹²³I- or ¹³¹I-MIBG.

are FDG-positive.¹⁴³ A recent study has reported higher FDG sensitivities for benign lesions (88%).²⁵ In malignant PHEO/PGL, FDG sensitivity ranges from 88% to 100% on a per-patient basis (Table 5). FDG appears to have the highest sensitivity in patients with succinate

dehydrogenase complex subunit B (SDHB) mutations.¹³⁵

Several small studies have evaluated the use of FDOPA in PHEO/PGL, with reported per-patient sensitivities of 88% to 100% (Tables 4, 5, and 6). In a

Table 5. Sensitivity for Detection of Malignant Pheochromocytoma/Paraganglioma

Reference	No. of Patients ^a	Patient-Based Sensitivity (lesion-based sensitivity in parentheses)						
		MIBG	SRS	FDG	FDA	FDOPA	CT	MRI
136	64	92.4% ^d						
142	17	82% ^f		88%				
172	14	57% ^e	87.5%					
140	53	70.6% ^e	88.9%		91.4%		100% ^b	100% ^b
176	9	75% ^d		89%		100%		
135	30	80% ^f		100%	88%			
141	34	85% ^f			97%		100%	100%
25	28	(57%) ^e		(74%)	(76%)	(45%) ^c	(100%) ^b	(100%) ^b
177	28			100%				
174	25					87.6%		
145	9					100%		
173	21	(56%) ^e				(73%)	(45%)	

^aData for malignant PGL only; some studies included both benign and malignant PGL.

^bStudies used either CT or MRI.

^cThis represents a mixed population; in SDHB the sensitivity of FDOPA was 20%, whereas in non-SDHB it was 93%.

^dIodine 131-MIBG.

^eIodine 123-MIBG.

^fEither ¹²³I- or ¹³¹I-MIBG.

Table 6. Sensitivity of Detection for Head and Neck Paraganglioma

Reference	Patient-Based Sensitivity (lesion-based sensitivity in parenthesis)				
	No. of Patients ^a	MIBG	SRS	FDOPA	CT MRI
148	15	46.7% (54%) ^d			
178	236	(38%) ^e			(95%) (100%)
152	117	(17.5%) ^d			
151	29	44% (42%) ^d	93% (89%)		93% ^c (82%) ^c
150	34		100% (94%)		
179	19		90%		
149	60		97%		
153	10			100% (100%)	100% (93%) ^b

^aData for head and neck patients only.^bThree lesions retrospectively identified on MRI after detection on PET.^cStudies used either CT or MRI.^dIodine 123-MIBG.^eEither [¹²³I]- or [¹³¹I]-MIBG.

comparison with MIBG, FDOPA detected 100% of benign lesions, whereas MIBG only detected 71%.¹⁴⁴ Similarly, Timmers et al reported a sensitivity of 81% for FDOPA compared to 77% for MIBG in benign tumors.²⁵ This is consistent with the finding that FDOPA combined with CT/MRI had a sensitivity of 94% compared to 74% using [¹²³I]-MIBG combined with CT/MRI.¹⁴⁵

A number of familial syndromes are associated with PGL, and it is increasingly recognized that these different genotypes are associated with a higher incidence of malignancies, extra-adrenal disease, and/or different imaging phenotypes. The major familial syndromes include MEN2A,B, VHL, neurofibromatosis 1 (NF1), and SDHx (x = B, C, and D) mutations. Unfortunately, most imaging studies have evaluated mixed populations, making it difficult to delineate the precise role of the various reagents in each syndrome. The study of Timmers et al was the first to recognize that in patients with malignant disease associated with SDHB, FDG imaging had the highest sensitivity (74% on a per-lesion basis) compared to 57% for [¹²³I]-MIBG, 76% for FDA, and 45% for FDOPA PET.²⁵ Taieb et al also showed high uptake and sensitivity of FDG in patients with SDHx mutations.¹⁴⁶ Thus, sensitivities reported in the literature for functional imaging in PHEO/PGL may vary significantly depending on the patient population being studied (Figure 2).

Head and Neck PGLs

Head and neck PGLs are rare tumors, the vast majority of which arise from the parasympathetic as opposed to the sympathetic nervous system. These tu-

mors have been referred to as chemodectomas, glomus tumors, and now, preferably, PGLs. They can be categorized according to site of origin, the most common being carotid body, glomus tympanic, and glomus jugular and, less commonly, vagal and other head and neck sites. These PGLs are generally slow-growing, non-hormone-secreting, and benign; 10% to 50% of cases are familial and associated with SDHx or VHL mutations and may be multicentric.¹⁴⁷ A small percentage of these tumors may be associated with catecholamine-producing tumors outside the head and neck.¹⁴⁸

Early diagnosis of head and neck PGLs is beneficial since lesions can grow large, causing destruction of adjacent structures and, over time, may metastasize. Because of the high incidence of multifocal disease, imaging is critical in staging. Initial imaging usually consists of anatomical studies, including CT and/or MRI. Functional imaging with SRS and FDOPA has been extremely useful. The role of other PET reagents has not been explored adequately.

The most extensively evaluated functional imaging modality for head and neck PGLs is SRS, with three large studies reporting sensitivities of 89% to 97% (Table 6).¹⁴⁹⁻¹⁵¹ Bustillo et al also reported a specificity of 82%.¹⁴⁹ Although ⁶⁸Ga somatostatin analogs are expected to perform better than SRS, only a few cases have been reported.

Studies using MIBG for head and neck PGLs have consistently observed low sensitivities ranging from 17.5% to 54% (Table 6). These detection rates are much lower than those for non-head and neck PGLs (Tables 4 and 5). For example, in a recent retrospective review, the

Figure 2. Patient with metastatic pheochromocytoma. MIBG shows multiple bone and liver lesions. All lesions seen in MIBG are better seen with fluorodopamine, which also shows additional lesions. Fluorodopa only demonstrates uptake in one lumbar spine bone lesion and in the liver. In contrast, FDG shows most of the bony lesions but fails to localize the liver lesion. These images demonstrate the heterogeneity of uptake of various reagents used in imaging of NET. Reprinted from Timmers et al.²⁵

sensitivity for head and neck PGLs was 17.5%, compared to 81.5% for those in the abdomen and thorax.¹⁵²

A small study of 10 patients with SDHD found that FDOPA had 100% sensitivity in head and neck PGL, and was superior to MRI.¹⁵³ In our own unpublished work, FDOPA had the highest lesion sensitivity (100%) compared to CT/MRI, FDG, SRS, FDA, and ¹²³I MIBG in a group of 23 lesions in nine patients, eight of whom had SDHB or SDHD mutations. In contrast, SRS had much lower sensitivity. Although case reports of FDG imaging look promising, no large series have been reported to date.¹⁵⁴

Thus, functional imaging is useful in the evaluation of PGLs, although some investigators believe it is unnecessary in patients with biochemical evidence of disease, no family history, and an adrenal lesion on CT/MRI.^{155,156} Which radiopharmaceuticals should be used depend on availability, patient genotype, and the information desired. If available, FDA PET/CT is the preferred technique for localization of primary PHEO/PGLs and to rule out metastases. However, since this is not generally available, FDOPA and [¹²³I]-MIBG scintigraphy are excellent alternatives. For head and neck primary tumors, FDOPA and SRS have high sensitivity. In SDHB, FDG appears to have the highest sensitivity. In cases where MIBG or radiolabeled somatostatin therapy is being considered, MIBG or SRS can be performed to assess for accumulation.

SUMMARY

There are a number of radiopharmaceuticals that are used to image NET. These reagents rely on cell surface

receptors or transporters and/or biochemical pathways, which differ among the various types of NET. Understanding these tumor characteristics and the mechanisms of uptake of each reagent will allow us to optimize imaging for each patient. The three main radiopharmaceuticals currently available in most facilities are SRS, MIBG, and FDG. Other reagents like FDOPA, FDA, and ⁶⁸Ga-labeled somatostatin analogs are very promising and their use will likely increase in the future as they become generally available. Other reagents have been used in the detection of NET but are either no longer used or are based on ¹¹C, which has a short half-life that makes it impractical since most facilities do not have a cyclotron on site.

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