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REVIEW

^{123}I-labeled metaiodobenzylguanidine for diagnosis of neuroendocrine tumors

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Abstract: Metaiodobenzylguanidine (MIBG) is an analog of the catecholamine norepinephrine. Through a type I energy-dependent active amine transport mechanism, it is taken up in presynaptic cytoplasmic storage vesicles of adrenergic nerves. Many normal tissues that have rich adrenergic innervation accumulate MIBG, including the heart and salivary glands. Additionally, MIBG is accumulated in benign and malignant tissues derived from the neural crest, such as the adrenal medulla and neuroendocrine tumors (NETs), where it is stored within neurosecretory granules. This provides the molecular basis for highly specific imaging and therapy with radiolabeled MIBG. Both ^{123}I-MIBG and ^{131}I-MIBG are available for diagnostic purposes. Considering the physical characteristics of ^{123}I (159 keV photon energy, 13.2 hours half-life) and clinical experience, ^{123}I-MIBG is the agent of choice for diagnostic imaging. It shows high sensitivity and specificity in detecting NETs. NETs include a wide range of neoplasms arising from tissues derived from the neural crest, such as neuroblastomas (NBs), pheochromocytomas, paragangliomas, NETs of the gastroenteropancreatic tract (GEP tumors), as well as medullary thyroid carcinomas (MTCs). The purpose of this review is to summarize the diagnostic application of ^{123}I-MIBG in detecting diverse NETs and in guiding the subsequent clinical management and treatment protocols.

Keywords: ^{123}I-MIBG, diagnosis, neuroblastoma, pheochromocytoma, paraganglioma, neuroendocrine tumors of the gastroenteropancreatic tract, medullary thyroid carcinoma, multiple endocrine neoplasm syndromes

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from tissues derived from the neural crest, such as the adrenal medulla, the pituitary and the parathyroids, parafollicular cells of the thyroid, endocrine islets of the pancreas, and endocrine cells in the respiratory and gastrointestinal tracts. Different NETs synthesize and secrete a diverse variety of peptide hormones and biogenic amines. Their clinical behaviors (eg, age, gender, incidence, and prognosis) are extremely variable. They may be functioning or nonfunctioning, ranging from very slowly growing tumors (well differentiated NETs which are the majority), to highly aggressive malignant tumors (poorly differentiated NETs).[1,2] On the basis of their biological, anatomical and clinical features, NETs are mainly classified into six different subtypes which are shown in Table 1.

It is well known that NET cells can take up neuroamines, as well as express peptide receptors and transporters on their cell membrane. By taking advantage of these features, many radiolabeled ligands targeting NET biomarkers have been developed for tumor imaging and therapy purposes. Metaiodobenzylguanidine (MIBG) is a small molecule

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Table 1 Classification of the neuroendocrine tumors

I. Tumors of sympathoadrenal lineage
—Neuroblastoma
—Pheochromocytoma
—Paraganglioma
II. Neuroendocrine tumors of the gastroenteropancreatic tract (GEPs)
—Carcinoids
  —Foregut carcinoids (stomach, duodenum)
  —Midgut carcinoids (jejunum, distal ileum, appendix, cecum, proximal colon)
  —Hindgut carcinoids (distal colon, rectum)
—Pancreatic endocrine tumors (PETs)
  —Gastrinomas, insulinomas, VIPomas, glucagonomas, somatostatinomas
III. Medullary thyroid carcinomas (MTCs)
IV. Multiple neuroendocrine neoplasia (MEN)
 —MEN 1 (hyperplasia or neoplasia of anterior pituitary, parathyroid gland, duodenopancreatic endocrine system; adenomas or hyperplastic nodules of adrenal and thyroid glands, multiple lipomas)
 —MEN 2
 —MEN 2A (MTC, pheochromocytoma, hyperplasia of parathyroid glands)
 —MEN 2B (rare parathyroid involvement; neuromas, musculoskeletal abnormalities, disturbances of intestinal motility)
 —FMTC
—other MEN syndromes
 (von Hippel–Lindau syndrome (VHL), the familial paraganglioma syndromes, Cowden syndrome, Carney complex, and hyperparathyroidism jaw–tumor syndromes)
V. Neuroendocrine tumors of the lung (Small cell lung cancers)
VI. Pituitary tumors

and a catecholamine analog. It is uptaken by presynaptic sympathetic nerves through an amine transporter, which usually recycles catecholamines, and stores in vesicles. Thus, MIBG can be taken up by NETs, in particular by catecholamine-secreting tumors such as neuroblastomas (NBs), pheochromocytomas, paragangliomas, endocrine tumors of the gastroenteropancreatic tract (GEP tumors), as well as medullary thyroid carcinomas (MTCs), which are originated from the neural crest and/or receive rich sympathetic innervation.[3]

MIBG has been labeled with radioiodines (^{123}I and ^{131}I). Compared with ^{131}I, ^{123}I displays distinct advantages for imaging. The 13.2 hour half-life and the lower 195 keV photon energy of ^{123}I allows for higher-quality single photon emission computed tomography (SPECT) and has a more favorable dosimetry. The adsorbed dose from ^{123}I for patients is lower, that is, the adsorbed dose from 370 MBq (10mCi) of ^{123}I-MIBG is equal to18.5MBq (0.5mCi) of ^{131}I-MIBG.[4] Therefore, ^{123}I-MIBG is the most suitable radiotracer to image most endocrine tumors of the sympathetic nervous system. However, to a certain extent, relatively higher cost limits widespread clinical use of ^{123}I-MIBG.[5] Thus, if ^{123}I is not available, ^{131}I-MIBG can be used as the alternative.

MIBG scintigraphy aids in the management of patients with tumors arising from the sympathetic nervous system in several ways.[6] First, MIBG findings can aid in the staging of a patient due to detection of sites of disease that were missed by other imaging modalities such as not found by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), or by determining that equivocal findings do not accumulate radiotracer and therefore do not represent sites of tumor involvement. Second, the accumulation of MIBG radioactivity can influence the choice of subsequent management the treatment in clinic. Third, the extent of MIBG uptake might have prognostic significance. However, it should be emphasized that the radiotracer may be taken up by normal liver, myocardium, spleen, lung, salivary gland, intestines, and thyroid (if inadequately blocked by supplemental iodine), and clinicians, need to distinguish normal tissue accumulation from disease involvement.

Because the majority of NETs overexpress high levels of the somatostatin (SS) receptor subtypes 2 and 5, radiolabeled SS analogues also have been used to target NETs *in vivo*, such as diethylenetriaminepentaacetic acid (DTPA)-D-Phe-octreotide (pentetreotide).[3,7] Several PET tracers are also gradually applied for diagnosis of NETs.

At present, nuclear medicine tests are an integral part of the management and treatment of patients affected by neuroendocrine tumors.[8] As new tracers are being developed, we anticipate that, nuclear medicine will play an important role in contributing to the study of NETs.

This article mainly reviews recent applications of ^{123}I-MIBG as a diagnostic agent in the detection of different NETs, including neuroblastoma, pdheochromocytoma, paraganglioma, neuroendocrine tumors of the gastroenteropancreatic tract, as well as medullary thyroid carcinoma.

Neuroblastomas

Neuroblastomas (NBs) arise from primordial neural crest cells that normally develop into the sympathetic nervous system. They display diverse clinical and biologic characteristics. Neuroblastomas are the most common solid tumor of infancy, and the second most common extracranial, highly malignant solid tumor of childhood.[9] More than 90% of the ~600 cases diagnosed annually in the United States are in children ≤5 years old, with a peak incidence at age 2–3 years. Many more cases escape detection because of spontaneous regression or spontaneous maturation into benign lesions.[10–17] The predominant location of neuroblastomas is the retroperitoneum, followed by the posterior mediastinum (20%), pelvis (<5%), and neck (<5%).[18] 60% of patients with neuroblastoma develop metastases, usually to the cortical bone, bone marrow, lymph nodes, and liver. It is rare to find disease involvement of the lung or brain.[19–21]

Neuroblastomas have a strong propensity to metastasize; therefore, an accurate assessment of the extent of the disease is crucial for the choice of treatment strategy and for determining prognosis.[3] Many clinical examinations are used in staging neuroblastoma: CT, MRI, ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scan, ^{123}I-MIBG scintigraphy, bone marrow biopsy, and urine catecholamine metabolite levels. The drawback of CT and MRI is that these studies do not image the whole body. This may lead to lack of detection of metastases in parts of the body that are not included in the field of view. Thus, proper staging and monitoring of patients with neuroblastoma is crucially dependent on scintigraphic studies. ^{99m}Tc-MDP bone scanning is the gold standard detecting neuroblastoma metastases in cortical bone. Compared with MIBG and PET, bone scanning has the disadvantage of showing cortical bone metastases only, which has decreased its application in recent years. However, given its superior sensitivity for revealing cortical osseous metastases, ^{99m}Tc-MDP bone scan still has an important ancillary role in staging and surveillance of neuroblastoma.[18,22–26]

Since the early 1980s, ^{123}I- (and ^{131}I-) labeled MIBG scintigraphy has gradually assumed an important role in the staging and monitoring of neuroblastoma. It has proven to have high sensitivity and specificity for the detection of primary and metastatic disease. Numerous studies show that ^{123}I-MIBG detects 90%–95% of neuroblastomas in primary sites as well as metastases in cortical bone, bone marrow, and lymph nodes,[27–29] however, sensitivity for lesions in the central nervous system (CNS) is less certain (Figure 1). It was reported that MIBG scans were negative in more than half of the patients with CNS metastasis, which was due in part to difficulty in discriminating CNS lesions from skull lesions with SPECT images and in part to some patients with meningeal disease without bulky lesions.[21] On the whole, MIBG imaging is today considered to be the most effective indicator for the presence of neuroblastoma.[18] Its major indications are: staging of the extent of the disease at presentation as well as restaging after treatment; detection of postsurgical residual tumor; monitoring the effect of treatment; and early diagnosis of recurrence at follow-up. Furthermore, it is essential as a prerequisite for ^{131}I-MIBG therapy.

^{18}F-FDG PET has recently emerged as a promising modality for detecting neuroblastoma in both soft tissue and skeleton. PET is particularly useful for detecting metastases in the liver, which may be obscured by physiologic uptake of radiotracer in the liver in MIBG scans. A major drawback of PET is the lack of visualization of lesions in the brain due to high physiologic metabolitic activity in brain. Also, inflammatory processes and other benign diseases accumulate FDG, which can result in false positive results.[18,25,30] Therefore, for patients with neuroblastomas, ^{18}F-FDG PET should be performed only if MIBG scintigraphy gives negative results and there is reasonable suspicion for the presence of disease.[3]

Pheochromocytoma and paraganglioma

Pheochromocytomas are rare, mostly benign neuroendocrime tumors arising from chromaffin cells. Normally, most chromaffin cells in human body gradually degenerate after birth. 90% of the surviving cells are situated in the adrenal medulla, the remaining 10% in paragangliar location adjacent to the abdominal aorta.

In the general population, pheochromocytomas occur at a frequency of 2 to 8 per million. The peak incidence occurs during the fourth and fifth decade of life, with equal gender distribution, and the prevalence in hypertensive patients is 0.2%–0.4%.[31–33] In addition to the obvious morbidity and mortality from this

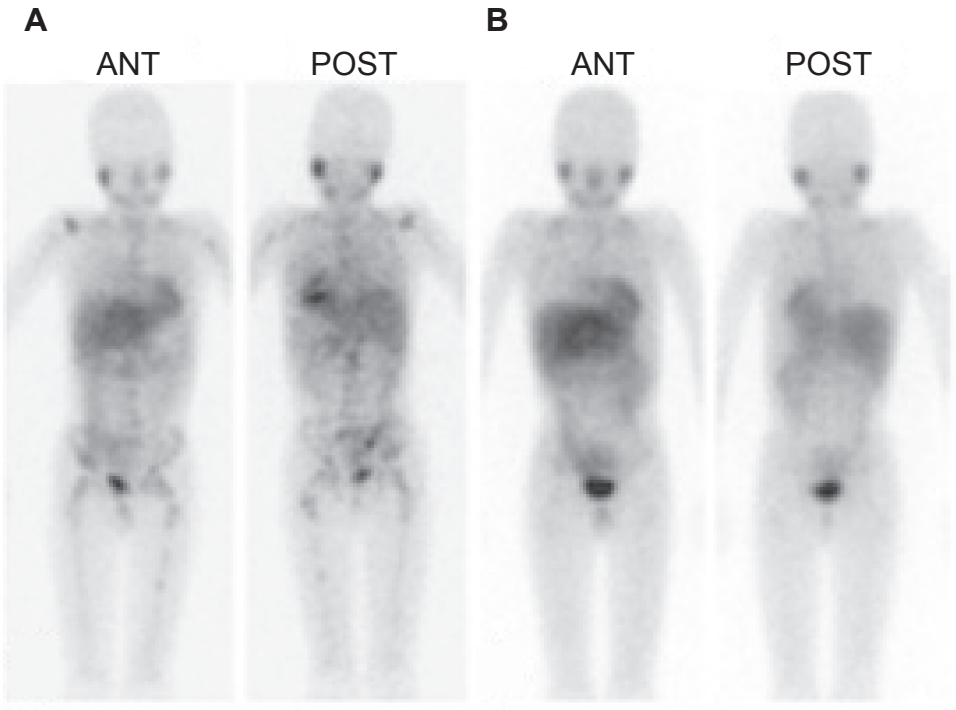

Figure 1 ^{123}I-MIBG scan pretherapy and on day +56 post therapy. Pretherapy scan (**A**) showed multiple sites of skeletal uptake throughout the spine, pelvis and femurs. The post-therapy day +56 scan (**B**) showed only very faint uptake in the left proximal humerus and left pelvis. Copyright © 2009. Reprinted by permission of American Society of Clinical Oncology from Matthay KK, Quach A, Huberty J, et al Iodine-131–Metaiobobenzylguanidine Double Infusion with Autologous Stem-Cell Rescue for Neuroblastoma: A New Approach to Neuroblastoma Therapy Phase I Study. *J Clin Oncol*. 2009; 27(7):1020–1025.

neoplasia, catecholamine production from pheochromocytomas may impair the function of end organs including heart, brain, and kidneys. Futhermore, pheochromocytoma patients have increased risk of developing additional tumors, such as liver carcinomas, or malignant melanoma.[34] Thus, early diagnosis and treatment of pheochromocytomas is especially important.

The laboratory diagnosis of pheochromocytomas depends on detection of biochemical markers of catecholamine overproduction in urine and/or plasma, such as VMA and norepinephrine. Localizing tumors is based on imaging methods, such as ultrasound, CT, MRI, and radionuclide imaging. Ultrasound is simple and noninvasive, but its accuracy is low. Both CT and MRI provide morphological imaging and reach relatively high sensitivity (90%–100%). However, their specificity is relatively low (70%–80%). Moreover, even in cases when CT and MRI are normal, the presence of early or small lesions without major morphological changes is not excluded.[35–38]

Despite the somewhat limited specificity of CT and MRI, identification of pheochromocytomas with imaging techniques can be achieved through use of the more specific ^{123}I-MIBG scanning. Many reports show a diagnostic sensitivity of 77%–90% for detection of pheochromocytoma, and a specificity of 95%–100%[36,38,39] (Figure 2). Even in asymptomatic patients with pheochromocytomas, ^{123}I-MIBG is often able to detect the tumor.[40] Therefore, ^{123}I-MIBG is the primary imaging method for presurgical staging and for evaluating response to therapy of pheochromocytoma.

However, several factors can cause false negative results of ^{123}I-MIBG scanning. These include interference with tracer uptake by the tumor by certain drugs (including tricyclic antidepressants, antihypertensives, cocaine, sympathomimetics including nasal decongestants containing phenylpropanolamine and calcium channel blocking medicines),[41] small tumor diameter (<1.5~2.0 cm, which would be below the resolution threshold of the respective camera used), and large areas of necrosis, and (or) hemorrhage within tumors that do not accumulate ^{123}I-MIBG.[42] In contrast, false positive findings can be caused by adrenal hyperplasia, adrenal adenoma or high injection dose (>10 mCi).

Pheochromocytomas, when found outside of the adrenal glands, are named paragangliomas or extra-adrenal pheochromocytomas. They are found predominantly in abdominal paraaorticbody (75%), followed by bladder (10%), thoracic locations (10%), head and neck, and pelvic locations (5%).[39]

Compared with CT and MRI, radionuclide scans image the whole body scan, which is especially useful for diagnosis of paragangliomas and metastatic disease (Figure 3). However, it emphasizes that the incidence

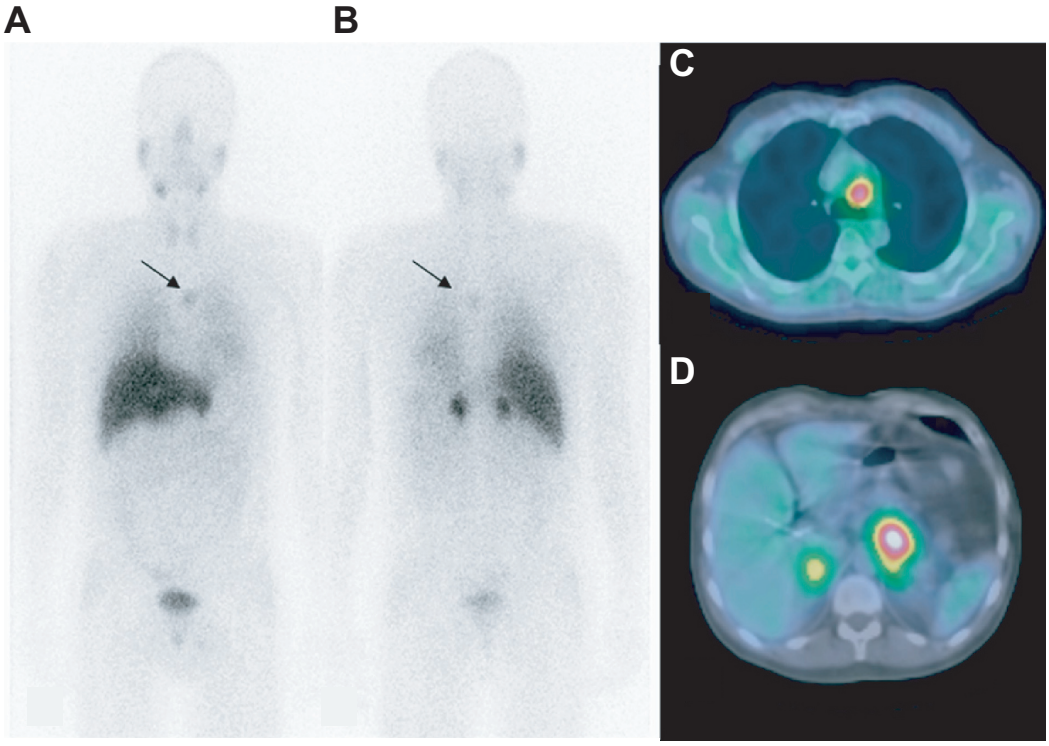

Figure 2 ^{123}I-MIBG scintigraphy performed in a hypertensive patient with bilateral adrenal pheochromocytomas. Anterior (**A**) and posterior (**B**) whole-body scintigraphy and fused SPECT/CT image (**D**) obtained with a hybrid machine clearly depict and correctly localize both pheochromocytomas. An unsuspected additional focus of uptake is seen in the thorax (arrow), and it is localized in the aortopulmonary window, as demonstrated by SPECT/CT images (**C**). Copyright © 2006. Reprinted by permission of Elsevier Inc. from Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. *Semin Nucl Med.* 2006; 36(3):228–247.

of malignant pheochromocytomas is 40% or more in patients with paragangliomas.[43] Rarely, ^{123}I-MIBG uptake of malignant pheochromocytoma is low, which may cause a false negative scan. In patients with negative ^{123}I-MIBG scans, who have a high index of suspicion for pheochromocytoma due to biochemical markers such as increased levels of catecholamines and their metabolites in the urine and/or plasma, other nuclear imaging techniques can be considered. ^{111}In-octreotide SPECT, as well as ^{18}F-fluorodeoxyglucose (FDG), ^{18}F-fluorodopamine (DOPA), ^{18}F-fluorodopa (DA), and/or ^{11}C-hydroxyephedrine (HED) PET all have complementary roles for the staging of pheochromocytomas and paragangliomas, especially in malignant tumors.[44–47] Moreover, ^{123}I-MIBG should be fused or compared to CT and MRI to assess vascular supply and invasiveness of tumors. This is particularly important for paragangliomas that involve or approach the abdominal artery, jugular vein and carotid artery.[43]

Approximately 20%–30% of pheochromocytomas are familial and caused by germline mutations.[48] Familial

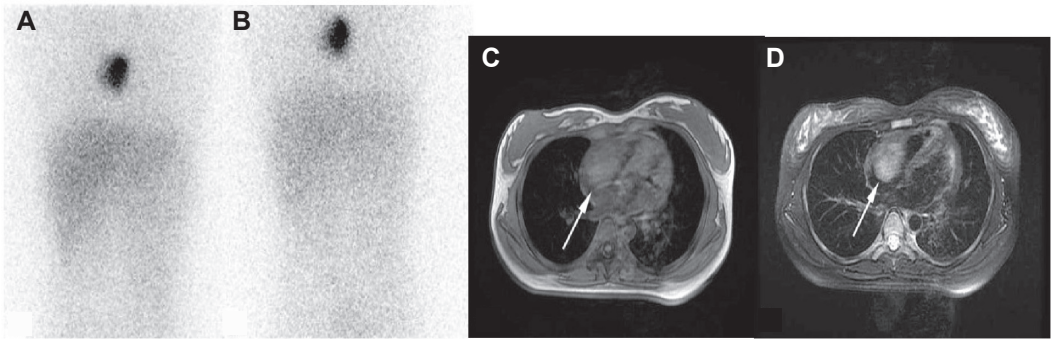

Figure 3 ^{131}I-MIBG scintigraphy in a 16-year-old girl with cardiac pheochromocytoma. Planar anterior images at 24 hours (**A**) and 48 hours (**B**) after injection. The result of radionuclide scan is concordant with MRI (**C** and **D**), which shows the mass locating in right atrium. Copyright © 2006. Provided by Ruijin Hospital, Shanghai, China. Published in *Chin J Nucl Med*. 2008; 28(4)

pheochromocytomas are frequently associated with other endocrine tumors, for example as part of multiple endocrine neoplasia (MEN) type 2. The clinical features of familial pheochromocytomas are somewhat different from those of sporadic: (1) Average age is younger in familial than in sporadic pheochromocytoma. (2) The incidence of bilateral or multifocal pheochromocytoma is higher in familial than in sporadic tumors (47% vs 10%). (3) Members of affected families usually have the similar age at onset of the disease and similar tumor location, most frequently in the adrenals. (4) Most familial pheochromocytomas are benign, without capsular invasion and without extra-adrenal metastases. (5) Paroxysmal hypertension is the main symptom, and 45% patients may be asymptomatic. (6) There is frequent coexistence of medullary thyroid cancer (MTC), c-cell hyperplasia, parathyroid hyperplasia, or ganglioneuroma.

Accordingly, in young patients with bilateral or multifocal tumors, the possibility of familial pheochromocytomas should be considered, and the patients and their family members should be followed long-term. ^{111}In-octreotide SPECT scans can also aid in the detection of familial pheochromocytomas.[49,50]

Neuroendocrine tumors of the gastroenteropancreatic tract

Neuroendocrine GEP tumors consist of a series of rare neoplasms arising from neuroendocrine cells within the gastrointestinal tract and pancreas. GEP tumors constitute ~70% of all NETs and ~2% of all tumors of the digestive system.[51] Classically, GEP tumors are classified as belonging to one of two main groups: Carcinoids and endocrine pancreatic tumors. Carcinoids are the most common and have traditionally been divided on the basis of the site of origin into foregut (stomach and duodenum), midgut (jejunum, distal ileum, appendix, cecum and proximal colon), and hindgut (distal colon and rectum). Endocrine pancreatic tumors (EPTs) are classified and named on the basis of hormone release and related clinical functional syndromes (ie, insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas). Nonfunctioning tumors represent approximately 15%–30% of all EPTs.[3] Gastrinoma is the most prevalent type of EPT, accounting for 10% of all GEP tumors.[52] With the exception of insulinomas, EPTs are malignant in most cases.[53] A recent WHO classification classifies NETs of the gastrointestinal tract according to morphological and biological findings at the time of diagnosis, with the aim of predicting tumor behavior and predicting prognosis. For each tumor site, neoplasms are divided into three groups: well-differentiated tumors with benign or uncertain behavior, low-grade malignancies, as well as highly malignant tumors.[2,54]

Most NETs secrete a variety of peptide hormones and amines. This may lead to diverse clinical syndromes including severe and potentially fatal diarrhea. In addition to bioactive hormones, NETs also excrete Chromogranin A (CgA), an important biochemical marker for diagnosis and follow-up.[55,56] Imaging methods are used to detect and localize the primary tumor and metastases. Imaging methods especially useful in localization GEP tumors are: ultrasound (US), endoscopic ultrasound (EUS), somatostatin receptor scintigraphy (SRS), CT, MRI, and angiography. Standard imaging modalities such as ultrasound, CT, or MRI are limited by the small size of lesions, the presence of multiple tumor sites, and large variability in tumor location.[3]

Most GEP tumors express SS receptors, with high expression levels within well-differentiated GEP tumors. Thus, somatostatin receptor scanning, rather than ^{123}I-MIBG scanning, is currently considered the imaging modality of choice, and the most reliable staging procedure.[3,57] In carcinoids, somatostatin receptor scanning has proved to be extremely useful for identifying the primary lesion and staging of the disease, particularly for midgut carcinoids, with reported sensitivities varying from 80% to nearly 100%.[3] (Figure 4). In EPTs, the sensitivity of radiolabeled SS analogs for the detection of gastrinomas, vasoactive intestinal polypeptide-secreting tumors, and glucagonomas as well as clinically nonfunctioning lesions ranges from 75% to nearly 100%, depending on the tumor type[58] (Figure 5). Insulinomas are the only exception, with a sensitivity $<$70%, due to lower levels of SS receptor expression on tumor cell membranes.[59,60]

Other peptide-based radiopharmaceuticals targeting CCK-B receptors have shown promise in initial studies, but have not yet reached widespread clinical use.[61]

In contrast to its dominant role in staging and follow up in pheochromocytoma, paraganglioma and neuroblastoma, there is the general agreement that ^{123}I-MIBG (or ^{131}I-MIBG) scanning plays a relatively limited role in the detection of neuroendocrine GEP tumors. About 40%–85% of patients with carcinoids may be detected by ^{123}I-MIBG scintigraphy.[62–66] Very few cases of EPTs treated with ^{131}I-MIBG have been reported, reflecting the relatively poor ^{123}I-MIBG uptake of these tumors. Primary and residual tumors are sometimes visualized, but the most striking imaging is that of carcinoid metastases in the liver, provided that SPECT with ^{123}I-MIBG is performed.[64,65] On the whole, scintigraphy with SS analogues is generally more sensitive than ^{123}I-MIBG scanning.

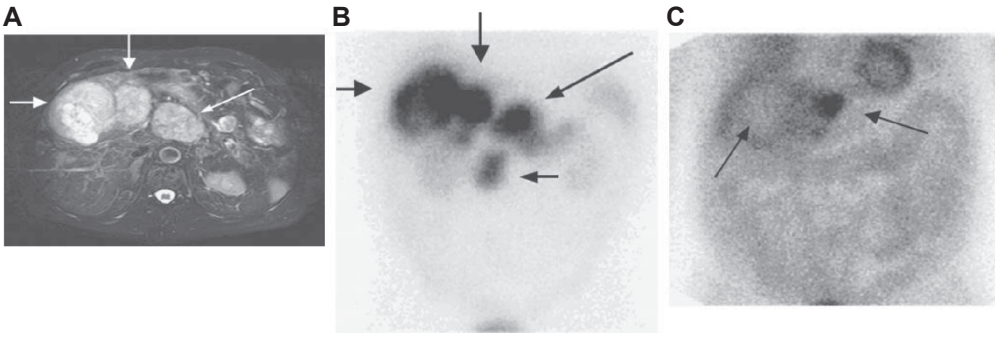

Figure 4 MRI (**A**), ^{111}In-pentetreotide (**B**), and ^{123}I-MIBG (**C**) scans of a patient with metastatic nonfunctioning P-NET demonstrate intense tracer uptake in liver and lymph node metastases and the large primary lesion (**A** and **B**, arrows). These findings are in contrast to the virtually negative MIBG scan, which shows only low uptake in 1 metastatic lesion in left liver lobe (**C**, arrow to right), with rest of tumor lesions being negative; note the cold area (**C**, thin arrow) in the right liver lobe corresponding to the major metastatic site. Copyright © 2006. Reprinted by permission of the Society of Nuclear Medicine from 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):223–233.

However ^{123}I-MIBG may occasionally detect lesions that are not visualized with somatostatin receptor scanning and serve as an adjunct imaging modality.[64,65,67]

Moreover, SS analogs labeled with positron emitting tracers have demonstrated great promise for diagnosis of endocrine GEP tumors. Due to the higher resolution of PET compared to SPECT, imaging of GEP tumors with positron emitter labeled SS analogs such as ^{64}Cu-TETA-OC, ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, and ^{68}Ga-DOTA-TATE, is showing very promising results.[68–71]

Medullary thyroid carcinomas

Medullary thyroid carcinomas (MTCs) are rare, malignant thyroid tumors. They originate from calcitonin-secreting parafollicular cells (C cells), which are embryonically derived from the neural crest. MTC is about 3%–10% of the mortality of all malignant thyroid tumors.[72] As the tumor is usually asymptomatic in early stages, MTCs tend to be diagnosed at later stages when metastases are present. Together with the lack of iodine uptake in these tumors, which precludes radioiodide therapy, this factor leads to a relatively poor prognosis of patients with MTC. Metastases are most commonly in locoregional lymph nodes within the neck (71%–80%), followed by mediastinal lymph nodes (36%), and distant metastases (20%).[73,74] Accurate location and early detection of metastatic lesions is crucial for making the proper treatment choice.

Helpful laboratory tests for diagnosis and surveillance of MTC include serum calcitonin, with or without pentagastrin stimulation, as well as carcinoembryonic antigen (CEA). Morphologic imaging methods, such as US, CT, and MRI, are helpful for staging, but may miss smaller lesions as well as metastases that are outside of the imaged body region. Because of high expression of somatostatin receptors on MTC cells, ^{111}In-pentetreotide has been proposed as a diagnostic tool for location of residual, recurrent, and metastatic MTC. ^{111}In-DTPA-octretoide imaging has been reported

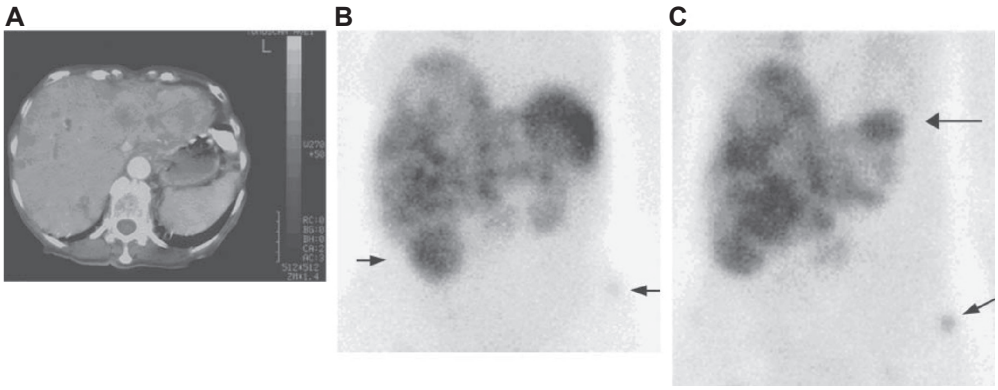

Figure 5 CT (**A**), ^{111}In-pentetreotide (**B**), and ^{123}I-MIBG (**C**) images of a patient with advanced functioning EC cell carcinoid show multiple metastases to the liver with intense uptake of both tracers. An additional site of uptake (**B**, left arrow) represents the right kidney. MIBG scan visualizes a hepatic lesion (**C**, upper arrow) which is obscured by physiologic splenic uptake on pentetreotide imaging. An osseous metastasis in the left pelvic bone (**B** and **C**, arrows to lower right) is also better visualized in the MIBG scan. Copyright © 2006. Reprinted by permission of the Society of Nuclear Medicine from 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):223–233.

to detect 29%–77% of MTC. Moreover, ^{18}F-FDG PET is a useful method for staging and follow-up of MTCs. Superior to other imaging technologies, ^{18}F-FDG PET showed the highest probability of detecting MTC, with high sensitivity (78%–95%) and specificity (~79%).[73,75,76]

Although the specificity of ^{123}I-MIBG taken up by MTC is high (>95%), the sensitivity is only 30%–60%,[77–81] lower than ^{111}In-DTPA-octretoide. Thus, ^{123}I-MIBG SPECT for detection of lesions is somewhat limited. However, ^{123}I-MIBG scintigraphy should be carried out in the following clinical situations:[8] (1) whenever the existence of a concomitant pheochromocytoma is suspected (as in a setting of multiple neuroendocrine neoplasia, see below), (2) MTC metastases take up high levels of MIBG, allowing for ^{131}I-MIBG radionuclide therapy, as well as (3) ^{123}I-MIBG imaging should be performed when evaluating the possibility of ^{131}I-MIBG treatment.

Multiple endocrine neoplasia syndromes

NETs can occur either sporadically or as part of familial syndromes called multiple endocrine neoplasia (MEN). MEN syndromes are rare autosomal-dominant conditions that predispose affected individuals to benign and malignant tumors of the pituitary, thyroid, parathyroids, adrenals, endocrine pancreas, paraganglia, or other nonendocrine organs. MEN syndromes differentiate between MEN type 1 (MEN 1) and MEN type 2 (MEN 2). Moreover, several other hereditary conditions may also be associated and need to be considered in the category of MEN syndromes: von Hippel–Lindau syndrome (VHL), the familial paraganglioma syndromes, Cowden syndrome, Carney complex, and hyperparathyroidism jaw-tumor syndromes.[82]

MEN 1 is characterized by benign or malignant tumors of the anterior pituitary, the parathyroid glands, and of the duodenopancreatic endocrine system, as well as by adenomas or hyperplastic nodules of adrenal glands and thyroid, and multiple lipomas. MEN 1 occurs as a result of inactivating mutations of the MEN1 gene, located on chromosome 11q13. Its prevalence is estimated to be 1 in 20,000 to 40,000 individuals.[83] Because most tumors that are part of MEN 1 syndrome are not catecholamine-secreting tumors, MIBG scans have limited value in imaging MEN 1. Rather, CT and MRI are routinely used in clinical practice.

MEN 2 is divided into three clinical subtypes: MEN 2A, MEN 2B, and familial MTC (FMTC). The hallmark of MEN 2 is a high lifetime risk of developing medullary thyroid carcinoma (MTC) of more than 95%.[82] MEN 2 occurs as a result of germline activating missense mutations of the RET proto-oncogene, located on chromosome 10q11.2. Its prevalence is about 1 in 35,000 individuals.[83] MEN 2A is the most common subtype of MEN 2 and is associated with MTC and the risk of developing pheochromocytoma (in approximately 50% of patients) or primary hyperparathyroidism (in 20%–30% of patients).[84] MEN 2B is the rarest subtype and is associated with MTC and the risk of pheochromocytoma (in approximately 50% of patients), as well as a pathognomonic physical appearance which results from mucosal neuromas in the tongue, lips and eyelids.[85] Patients with FMTC develop MTC, but are not at increased risk for other tumors. Only families in which four or more cases of MTC exist with documented absence of pheochromocytoma and hyperparathyroidism should be considered as for FMTC.[86]

Once an index patient has been identified, RET protooncogene genetic testing is the diagnostic standard of families with MEN 2 syndrome. Hormone levels such as calcitonin are used as tumor markers, and are employed alongside imaging studies to follow patients with existing neoplasias. MEN 2 syndromes have similar biological and clinical features to those of catecholamine secreting neuroendocrine tumors that are derived from the sympathetic nervous system, such as familial pheochromocytomas. ^{123}I-MIBG is the primary, most effective imaging test for evaluating MEN 2 syndrome (Figure 6). Radiolabeled SS analog scintigraphy and ^{18}F-FDG PET may be considered as complementary imaging modalities.

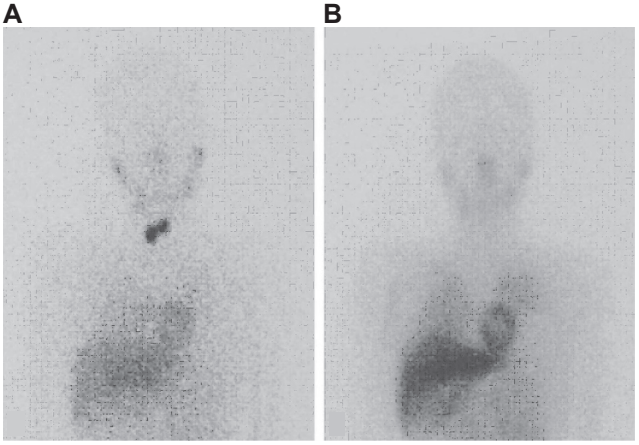

Figure 6 Preoperative and postoperative findings of ^{123}I-MIBG scintigraphy in a 14-year-old female with MEN 2B and recurrent MTC. She had previously undergone total thyroidectomy at 7 years of age, followed by three neck dissections for tumor recurrence. Preoperatively, ^{123}I-MIBG uptake is noted in the central neck region 24 hours after injection of 100 MBq of ^{123}I-MIBG (**A**). Postoperatively, no increased uptake of ^{123}I-MIBG can be identified at 24 hours after injection (**B**). Copyright © 2005. Reprinted by permission of Elsevier Inc. from Shimotake T, Tsuda T, Aoi S, et al. Iodine 123 metaiodobenzylguanidine radio-guided navigation surgery for recurrent medullary thyroid carcinoma in a girl with multiple endocrine neoplasia type 2B. *J Pediatr Surg*. 2005; 40(10):1643–1646.

Conclusion

In conclusion, ^{123}I-MIBG scintigraphy has varying degrees of diagnostic value in NETs deriving from the sympathetic nervous system, depending on the specific tumor in question.^{123}I-MIBG is the primary, most effective imaging modality for neuroblastoma, pheochromocytoma, and paraganglioma. For endocrine tumors of the gastrointestinal tract, EUS and radiolabeled (eg, ^{111}In, ^{99m}Tc, ^{64}Cu, ^{68}Ga) SS analogs are preferable to ^{123}I-MIBG scanning. Compared with ^{18}F-FDG PET and radiolabeled SS analogs, ^{123}I-MIBG shows lower sensitivity for the detection of medullary thyroid carcinomas. ^{123}I-MIBG scans play a marginal role in several other tumors fitting the category of NETs, such as small cell lung cancer, or pituitary tumors, as evidenced by the scarceness of reports in the literature. Moreover, the imaging background of FDG PET in the obese patients is indeed high, and imaging quality is poor due to no metabolism of glucose in fat cells (except the brown fat). And ^{123}I-MIBG imaging could avoid this problem.

Table 2 lists "the first choice" radiopharmaceutical/modality in neuroendocrine tumors on the basis of the literatures and routine clinical protocols. However, it should be emphasized that "the first choice" is likely to be changed according to the clinical situation, the biology of the tumor and other clinical issues. And the development of nuclear medicine can also largely change "the first choice".

Of course, the diagnosis of neuroendocrine tumors has to be based on integrated information obtained from different imaging examinations. As a molecular imaging technique, the functional information supplied by ^{123}I-MIBG scans complements that of morphological imaging techniques, such as ultrasound, CT and MRI. Conceivably, ^{123}I-MIBG imaging could detect abnormal functional information before anatomical changes occur or reach a level of abnormality that allows for clinical diagnosis. ^{123}I-MIBG scans have become an invaluable tool for diagnosis, staging, and restaging, patient follow-up, treatment planning, and treatment monitoring of NETs, and routinely guide clinical practice. The introduction of hybrid scanners, such as SPECT/CT or PET/CT, which combine functional imaging with anatomical imaging, as well as development of more specific imaging agents with excellent high-contrast, will hopefully bring significant improvements in the diagnosis and treatment of NETs.

Table 2 First-choice radiopharmaceutical/modality in neuroendocrine tumors

Tumor type	First choice
Neuroblastoma	^{123}I-MIBG SPECT*
Pheochromcytoma	^{123}I-MIBG SPECT*
Paraganglioma	^{123}I-MIBG SPECT*
Gastroenteropancreatic(GEP) tumors	^{111}In-pentetreotide
Medullary thyroid carcinoma	^{18}F-FDG PET
MEN 1	—#
MEN 2A	^{123}I-MIBG SPECT*
MEN 2B, FMTC	^{18}F-FDG PET
Neuroendocrine lung cancer	^{18}F-FDG PET
Pituitary tumors	—#

Notes: *If ^{123}I is not available, ^{131}I could be used as the alternative; #Radionuclide scintigraphy is not the first-choice imaging method.

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