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## Scintigraphic Evaluation of Neuroendocrine Tumors

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### Introduction

Neuroendocrine tumors arise from cells that originate in the neural crest. Although these cells have a common embryological origin, they are distributed to various sites and organ systems throughout the body, where they can give rise to a variety of tumor types that are related by their common embryological origin. These cells share a characteristic feature of the ability to produce peptide hormones and the ability to synthesize amines from certain precursors, which gave rise to the concept known as Amine Precursor Uptake and Decarboxylation.<sup>[1]</sup> These cells were referred to as APUD cells. Collectively, the tumors that arose from these cells were classified by Pearse as APUDomas, currently more commonly referred to as neuroendocrine tumors.

The APUD cells produce peptides and amines that act as hormones or as neurotransmitters throughout the body. These APUD cells reside in various organ systems such as the pituitary gland, the pancreas, the adrenal medulla, the thyroid gland, and the gastrointestinal tract. Regulatory peptides that are released by neuroendocrine cells may function as hormones, neurotransmitters, or as paracrine hormones. The discovery that characteristic amines and peptides associated with these APUD cells were present in the central nervous system and the peripheral nervous system resulted in the formulation of the term *neuroendocrine* to highlight the association between the neural and endocrine systems.

Neuroendocrine tumors include such tumors as adenomas from the pituitary gland, islet cell tumors from the pancreas, pheochromocytoma and neuroblastoma from the adrenal medulla, medullary thyroid carcinoma from the C-cells of the thyroid gland, carcinoid tumors from the gastrointestinal tract (or less often from the lung), and paragangliomas.

Generally, anatomic and/or physiologic-functional imaging for neuroendocrine tumors is reserved for patients who present with a clinical history that is suspicious for a neuroendocrine tumor, supported by elevated levels of primary hormones and/or metabolites in the plasma and/or urine. These patients can be evaluated by anatomical imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI), and the functional status of these tumors can be assessed by physiologic imaging via scintigraphy, with agents such as radiolabeled meta-iodobenzylguanidine or radiolabeled octreotide. These imaging techniques should be considered as complementary studies, rather than competitive modalities, as each provides important aspects in the evaluation of these underlying tumors for patient management. The remaining discussion will focus on the scintigraphic evaluation of these tumors.

### Meta-iodobenzylguanidine

Radiolabeled meta-iodobenzyl-guanidine (MIBG) is an agent that was synthesized at the University of Michigan.<sup>[2]</sup> As early as 1980, this radiopharmaceutical was found to concentrate in sufficient amounts to visualize the adrenal medullas of dogs and monkeys scintigraphically,<sup>[3,4]</sup> which laid a foundation for pursuing scintigraphic imaging in man. Subsequently, I-131-labeled MIBG was used successfully for visualizing benign and malignant pheochromocytomas<sup>[5]</sup> and adrenal medullary hyperplasia. Subsequently, I-131 MIBG imaging has been extended to scintigraphic visualization of other tumors, such as carcinoid tumors and neuroblastoma, and has been employed

as a therapeutic agent in selected neuroendocrine tumors.<sup>[6-11]</sup>

Iodine-131 MIBG is an analog of guanethidine, and its molecular structure shares some characteristics with the adrenergic hormone-neurotransmitter, norepinephrine.<sup>[12]</sup> Norepinephrine is synthesized by normal adrenergic neurons and cells in the adrenal medulla, is stored in adrenergic granules, and is secreted by exocytosis. Some of the norepinephrine that is secreted is taken up by the same adrenergic cells and stored again in granules. During this uptake process, I-131 MIBG can enter the metabolic pathway of norepinephrine. The scintigraphic distribution of I-131 MIBG would be expected to occur in organs with adrenergic innervation, and in organs that process catecholamines for excretion, such as the liver and urinary bladder.

In order to effectively block the thyroid uptake of I-131, patients scheduled for an I-131 MIBG scan should receive super-saturated potassium iodide (SSKI) for 1 day prior to, and 6 days after, the injection of I-131 MIBG. The administered average dose of I-131 MIBG is 2.0 mCi (74 MBq). Whole-body anterior and posterior images are acquired at 48 hours.

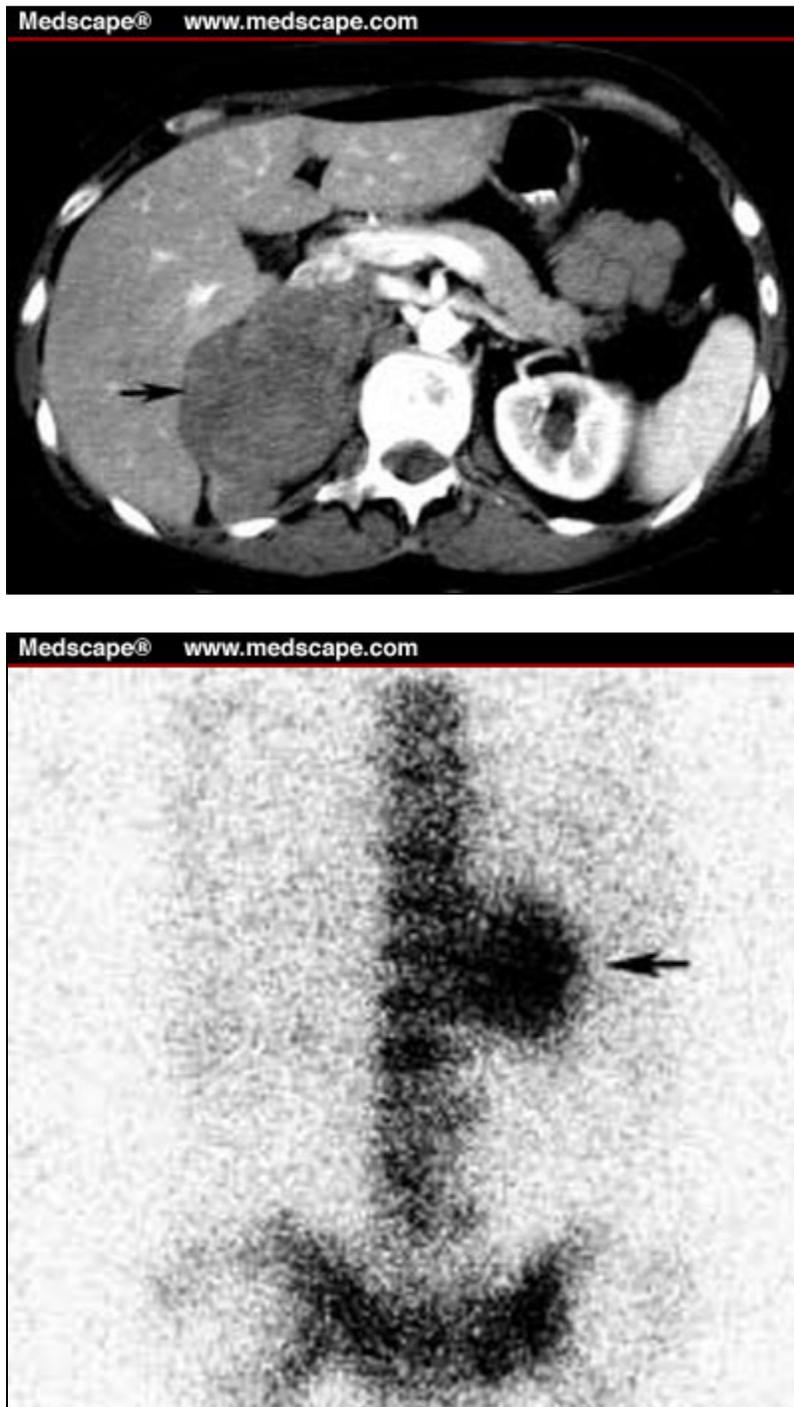
In a normal I-131 MIBG whole-body scan, the organs that will be visualized most frequently include the salivary glands, liver, spleen, and urinary bladder<sup>[13]</sup> (figure 1). Uptake of I-131 MIBG in the salivary glands and the spleen is likely related to the sympathetic innervation of these organs. Visualization of the liver is likely related to its volume and vascularity. Some liver uptake of I-131 MIBG may occur since the liver is a major site for catecholamine degradation. The urinary bladder is visualized as a result of the renal excretion of I-131 MIBG. Organs that are visualized less frequently, and less intensely, include the myocardium, lungs, kidneys, and normal adrenal glands. Typically, the thyroid gland is not seen in patients who are blocked with pretreatment of SSKI. The colon can be seen to a variable extent, which may be related to biliary and/or pancreatic excretion, secretion across the gastrointestinal epithelium, and swallowed saliva containing I-131 MIBG.



**Figure 1.** Normal biodistribution of I-131 MIBG is demonstrated in the nasopharynx, salivary glands, liver, spleen, and urinary bladder. Faint tracer accumulation is seen in the abdomen that conforms to expected bowel activity.

Tumors that were imaged initially with I-131 MIBG share a common embryological origin, arising from cells in the

neural crest. Although there are some discrepancies, these tumors share many characteristics, including the presence of neurosecretory granules that are capable of accumulating I-131 MIBG. This common characteristic led to attempts at imaging pheochromocytomas, carcinoid tumors, neuroblastomas, and medullary carcinoma of the thyroid gland. There has been variable success of imaging these various tumors with I-131 MIBG (figure 2).



**Figure 2.** A 44-year-old woman presented with back pain. (A) A CT scan demonstrated a large right suprarenal mass (arrow). (B) A 48-hour delayed I-131 MIBG scan demonstrated a large focus of tracer accumulation (arrow) that corresponds to the mass. In addition, there is diffusely abnormal skeletal accumulation of tracer, consistent with osseous metastases. Pathology revealed a ganglioneuroblastoma.

The sensitivity of MIBG imaging for the detection of pheochromocytoma has ranged from 80% to 90%.<sup>[6]</sup> The explanation for the failure of proven pheochromocytomas to accumulate I-131 MIBG is unresolved. The lack of localization could result from alterations anywhere along the pathway of uptake, storage, or secretion in either the primary tumor or in a metastatic site. There does not appear to be a relationship between I-131 MIBG accumulation and either the location or the histologic makeup of the tumor. A direct proportional correlation has been shown between the percentage uptake of I-131 MIBG and the number of secretory granules identified in tissue sections, which is not a good indicator of the tumor's secretory status, but is a good indicator of the amount of stored hormone. Therefore, high uptake of MIBG by pheochromocytoma may occur in those tumors that contain abundant hormone, while low uptake of MIBG may occur in those tumors with less hormone.

In the evaluation of carcinoid tumors, in a study from our medical center, 48 of 82 patients (59%) demonstrated abnormal accumulation of I-131 MIBG in the primary tumor or a distant metastatic site.<sup>[9]</sup> The success of imaging varied from 80% of tumors arising from the pancreas (4 of 5 patients) to only 11% of carcinoids arising from the bronchus (1 of 9 patients). In a subgroup of 41 patients who had elevated serum serotonin levels, regardless of the origin of their tumor, 80% had abnormal accumulation of I-131 MIBG. The explanation of variability in I-131 MIBG uptake in carcinoid tumors also remains unresolved. The known biologic differences in tumors arising from foregut, midgut, or hindgut, such as the electron microscopic appearance of their neurosecretory granules, pattern of distant metastases, or neurohumoral secretory characteristics, do not provide an adequate resolution of this question. As in the case of pheochromocytoma, the lack of localization could result from alterations anywhere along the pathway of uptake, storage, or secretion in either the primary tumor or metastatic site.

Neuroblastoma has been successfully imaged with I-131 MIBG, with a cumulative sensitivity for detection of tumor indicated from reported studies of around 91%.<sup>[14-16]</sup> Other tumors, such as a medullary carcinoma of the thyroid gland, paragangliomas, and a polypeptide-gastrin-serotonin-secreting pancreatic tumor, have been described, but to a lesser extent than the more commonly imaged pheochromocytomas and carcinoid tumors.

## **Indium-111 OctreoScan**

A second scintigraphic technique for the identification and localization of neuroendocrine tumors is via the administration of In-111-labeled OctreoScan (Mallinckrodt Medical, Inc., St. Louis, MO). The success of scintigraphic imaging with this agent is based upon the physiology of somatostatin receptors.

Somatostatin is a naturally occurring cyclic neuropeptide consisting of 14 amino acids that was discovered as a growth hormone release inhibitory substance in the hypothalamus.<sup>[17]</sup> Somatostatin is an inhibitory peptide in several organ systems, where it inhibits several physiologic functions such as neurotransmission, the secretion of growth hormone and thyrotropin-stimulating hormone, gastric acid production, gastrointestinal motility, enzyme secretion from the pancreas, and insulin and glucagon secretion.<sup>[17,18]</sup> The effects of somatostatin are mediated by interaction with somatostatin receptors on different target cells. Somatostatin receptors are found in the cells of neuroendocrine organs and in some non-neuroendocrine cells. In addition, tumors that arise from these tissues also contain somatostatin receptors. Almost all neuroendocrine tumors possess a high density of somatostatin receptors. Certain non-neuroendocrine tumors, including meningiomas, well-differentiated brain tumors, malignant lymphomas, renal cell carcinoma, and carcinoma of the breast and lung have also demonstrated somatostatin receptors.

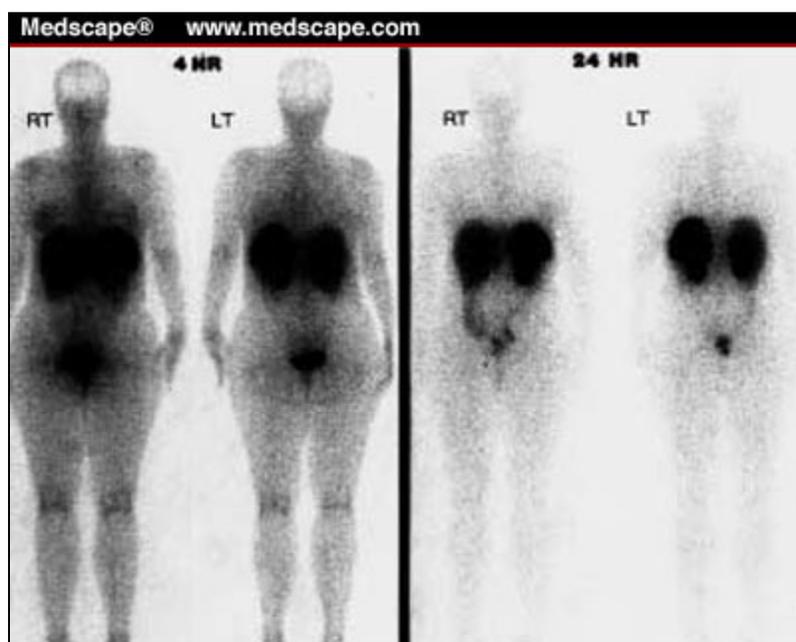
By possessing an ability to inhibit secretion of various hormones, it was postulated that somatostatin could be used therapeutically to alleviate symptoms and, perhaps, inhibit tumor growth. The success of using native somatostatin, however, was compromised by certain characteristics of this neuropeptide, predominantly by its short biological half-life of less than 3 minutes, and the occurrence of post-infusion rebound hypersecretion of hormone. With these limitations, attempts were made to synthesize an analog of somatostatin that would maintain its beneficial pharmacologic effect while avoiding its major disadvantages. This research led to the development of octreotide (Sandostatin, Novartis Pharmaceuticals Corp., East Hanover, NJ), the first commercially available analog that would bind to somatostatin receptors on tumors to suppress hypersecretion of hormones from endocrinesecreting tumors. Octreotide is protected against enzymatic degradation, possesses a half-life of approximately 2 hours, and does not produce a postadministration rebound hyper-secretion of hormone.

Subsequent to the development of octreotide, which would bind to somatostatin receptors, attempts were made to radiolabel this agent in order to visualize the high-density somatostatin receptors present in tumors. In 1987, researchers from the University Hospital Dijkzigt Rotterdam introduced I-123-labeled Tyr-3 octreotide. Using this agent, neuroendocrine tumors could be visualized, *in vivo*, based upon the identification of somatostatin receptors.<sup>[19-21]</sup> However, disadvantages of this particular agent included limited availability, the expense and short half-life of

I-123, a difficult labeling chemistry, and a high abdominal background of radioactivity, due to the principle clearance of this agent through the liver.

To overcome the difficulties associated with I-123 Tyr3-octreotide, a second radiolabeled analog of octreotide was developed, which was formulated by conjugating diethylene triamine penta-acetic acid (DTPA) to the basic octreotide molecule, which allowed radiolabeling by chelation with Indium-111.<sup>[22]</sup> This radiopharmaceutical, known as OctreoScan, is excreted mainly by the kidneys, with 90% of the dose being present in the urine within 24 hours of injection. The preferential renal excretion allows for clearer visualization of abdominal tumor sites, with less background activity. Although there is minor hepatobiliary excretion, the abdominal background is much less of a problem with OctreoScan than with I-123 Tyr3-octreotide. With its relatively long effective half-life, OctreoScan has been shown to be very successful in visualizing somatostatin receptor-bearing tumors after 24 to 48 hours, when interfering background radioactivity is minimized by renal clearance.

The administered average dose of In-111 OctreoScan is 6.0 mCi (222 MBq). The patient should be well hydrated with ample fluid intake prior to, and for 1 day after, radiopharmaceutical injection to increase the renal excretion of radiopharmaceutical, and to reduce radiation dose. Whole-body anterior and posterior images are acquired at 4 hours and 24 hours. An optional SPECT scan can be acquired at 24 hours. Although only approximately 2% of the administered dose undergoes hepatobiliary excretion, there are instances in which consideration for a standard bowel prep with a mild laxative may be considered prior to abdominal imaging. If necessary, imaging may also be performed at 48 hours, if there is difficulty in differentiating a tumor from normal bowel activity. The normal biodistribution of In-111 Octreo-Scan includes the liver, spleen, kidneys, and urinary bladder (figure 3).

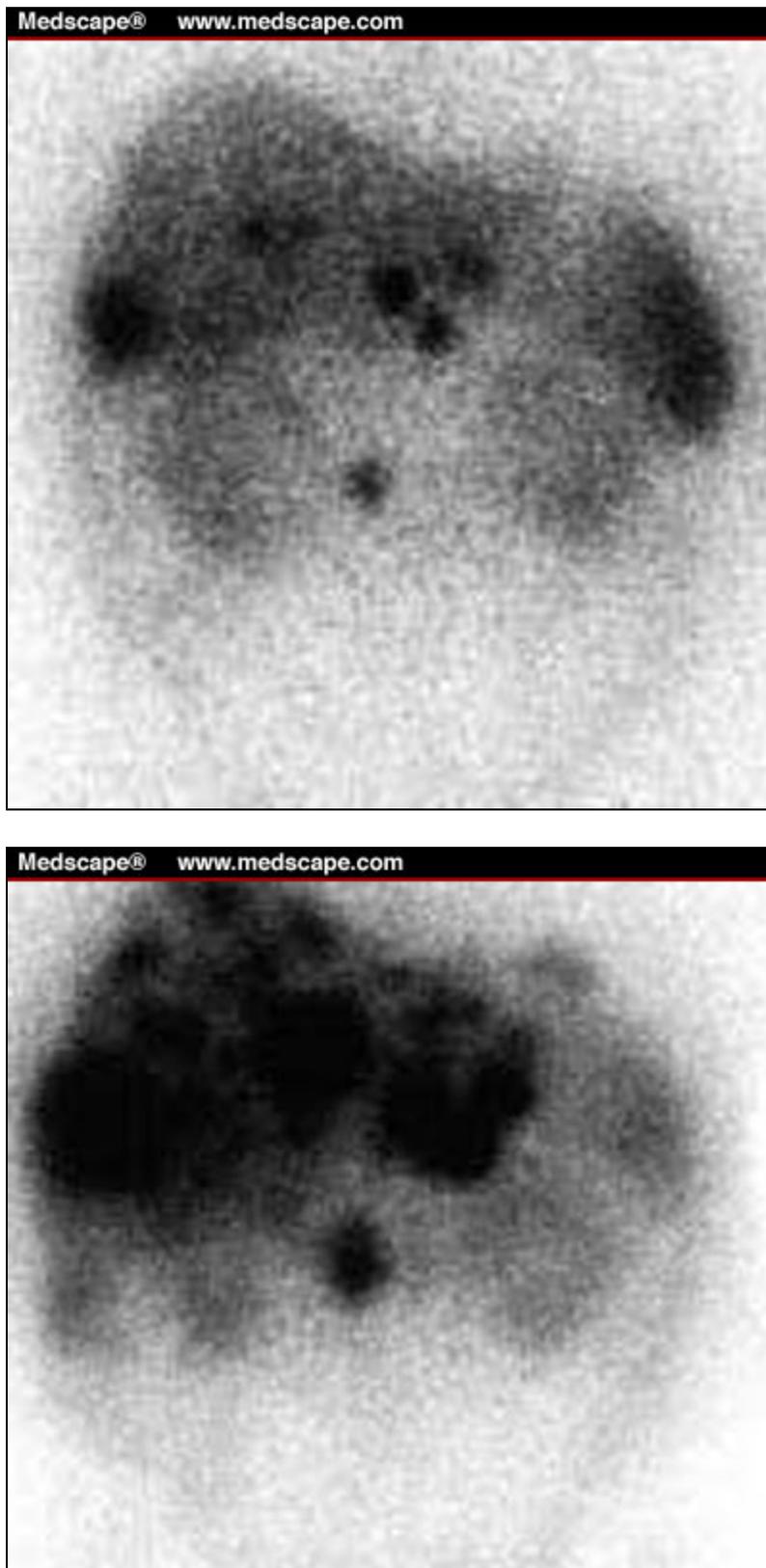


**Figure 3.** Normal biodistribution of In-111 OctreoScan is demonstrated in the liver, spleen, kidneys, and urinary bladder at 4 hours. Faint activity is also seen in the breasts. By 24 hours, minimal activity can also be identified in the bowel.

OctreoScan binds to somatostatin receptors in tissues throughout the body, but concentrates in tumors that contain a higher density of somatostatin receptors. A variety of tumors have been demonstrated with this agent.<sup>[23-25]</sup> OctreoScan is highly sensitive for the detection of carcinoid tumors (figure 4), with reported sensitivities of 80% to 100%. Pheochromocytoma and neuroblastoma, likewise, are highly detected with OctreoScan, with reported sensitivities of around 87% and 89%, respectively. Under protocols with variability in the dose of administered radiopharmaceutical and scanning techniques, sensitivities reported for the detection of gastrinomas (figure 5) have varied from 60% to 90%. Additional tumors that have been imaged with OctreoScan include insulinomas, pituitary tumors, paragangliomas, and medullary carcinoma of the thyroid gland.



**Figure 4.** A 73-year-old woman presented with abdominal pain. Ultrasound of the gall-bladder demonstrated hyperechoic lesions in the liver; subsequent abdominal CT scan confirmed rim-enhancing lesions in the right hepatic lobe, which, on biopsy, were consistent with carcinoid tumor. A 24-hour delayed whole-body OctreoScan image demonstrated abnormal hepatic, paraaortic and pelvic tracer accumulation, compatible with carcinoid metastases.



**Figure 5.** A 57-year-old man with gastrinoma. (A) A 48-hour delayed OctreoScan image demonstrated discrete foci of abnormal tracer accumulation in the region of the pancreas, the liver and a right para-aortic lymph node. Despite medical therapy, serum gastrin levels continued to rise. (B) A repeat 24-hour OctreoScan, acquired 3 months later, demonstrated the extent of marked interval progression of

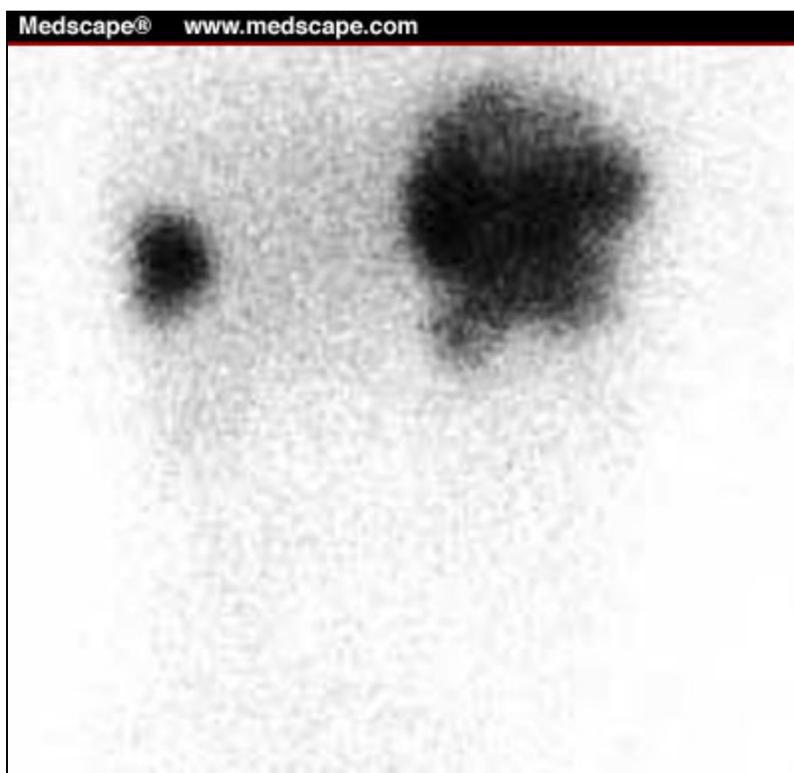
disease, with evidence of extensive hepatic metastases.

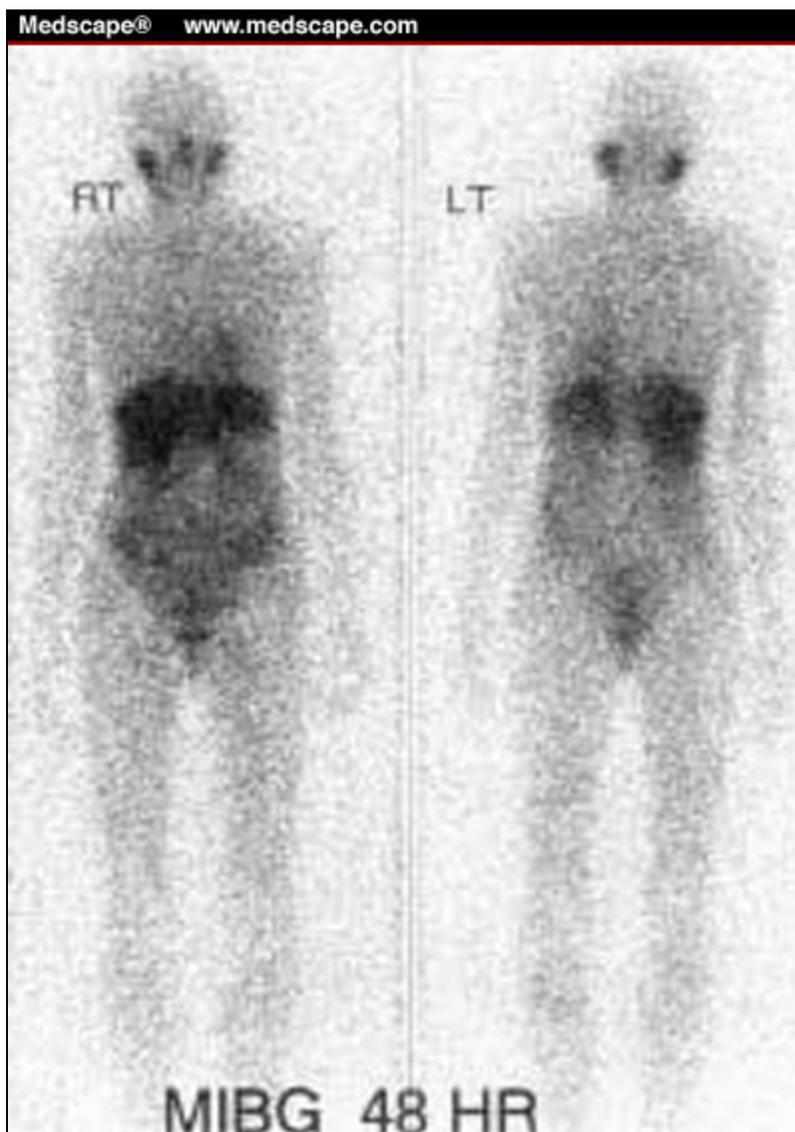
The sensitivity of OctreoScan imaging may be reduced in patients who are concurrently receiving therapeutic doses of Sandostatin. Temporary suspension of octreotide therapy, in consultation with the patient's referring physician, should be considered prior to OctreoScan administration. If it is not possible to temporarily withhold octreotide, imaging may still be attempted, even while the patient is maintained on therapy. Octreotide has been shown to produce severe hypoglycemia in insulinoma patients. Since OctreoScan is an analog of octreotide, intravenous glucose should be administered before and during OctreoScan administration to patients who are referred for scintigraphic evaluation of suspected insulinoma.

### Benefits of Neuroendocrine Tumor Scintigraphy

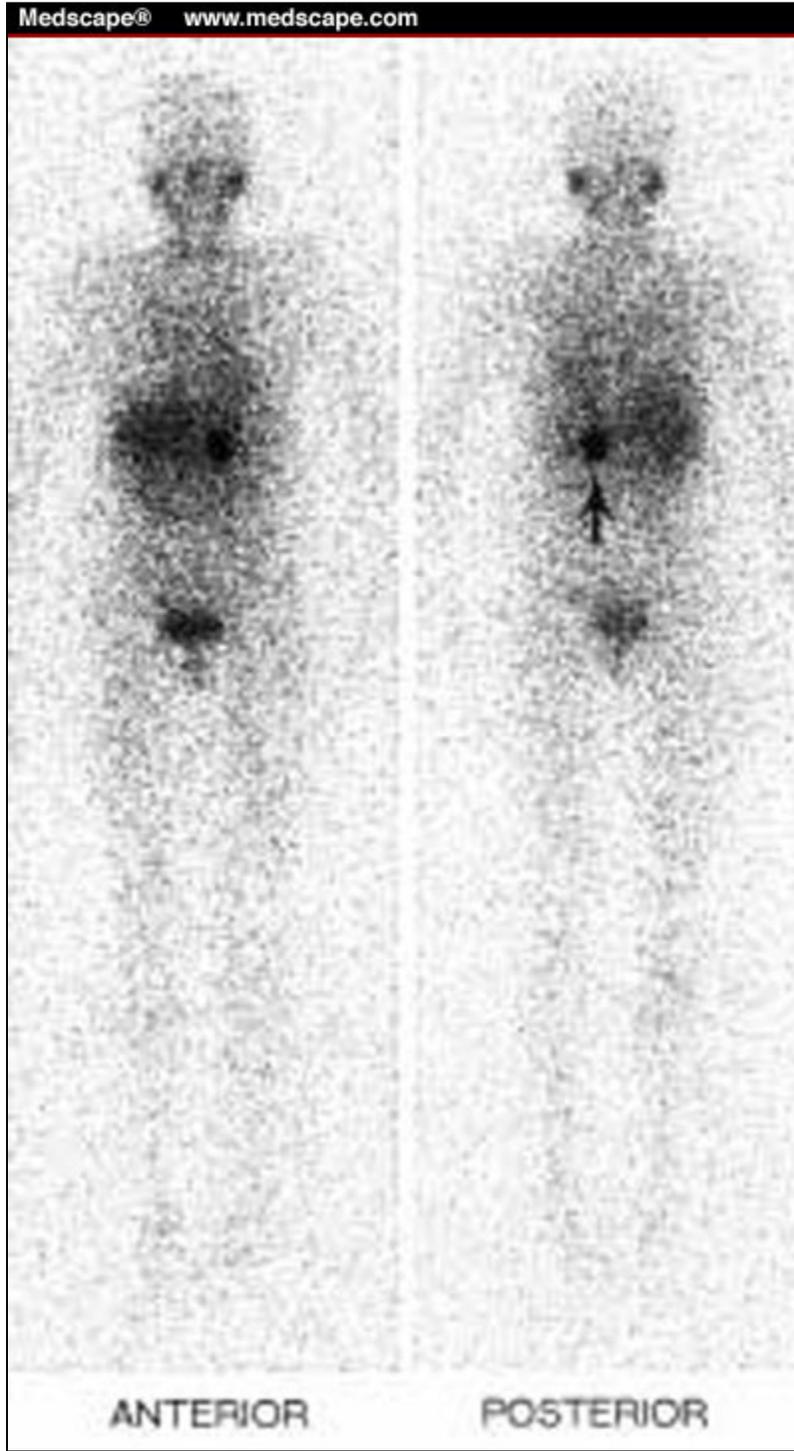
Many neuroendocrine tumors can be visualized successfully with I-131 MIBG or In-111 OctreoScan<sup>[26-29]</sup> (Table 1). These agents are taken up by normal tissues and by the neuroendocrine tumors by different mechanisms, as described above. Scintigraphic imaging complements, rather than competes directly with, anatomical imaging studies, such as CT or MRI. There are several indications for the use of scintigraphic imaging in the evaluation of neuroendocrine tumors.

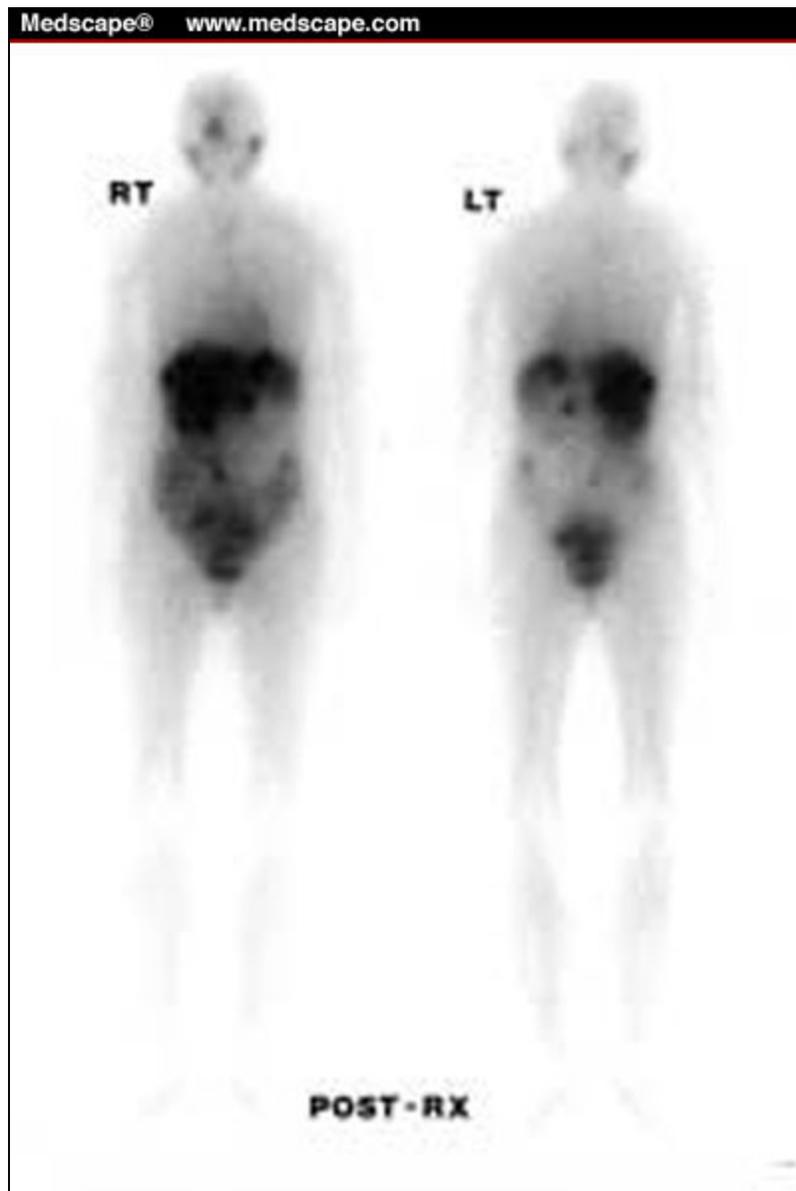
Scintigraphic studies can be complementary in those instances in which the anatomical imaging study is equivocal. In addition, scintigraphy can add specificity and increased confidence in a noninvasive diagnosis of a mass on CT or MRI that is suspicious for a primary or metastatic neuroendocrine tumor. In some instances, such as suspected pheochromocytoma, scintigraphy may be considered as the first imaging technique in the patient's evaluation. In addition to localizing sites of disease, scintigraphy of neuroendocrine tumors can provide a functional assessment of the disease state. With whole-body imaging capability, nuclear imaging is an excellent technique for searching for distant metastases or multifocal disease. Scintigraphy can also evaluate for tumor recurrence, for example, in evaluating abnormalities such as suspected scar tissue versus a recurrent tumor at or near a postoperative site (figure 6), and can also evaluate the efficacy of therapeutic interventions. Finally, scintigraphy can be performed to evaluate tracer uptake characteristics of a tumor when there is consideration of radionuclide therapy, such as high-dose I-131 MIBG therapy<sup>[30-33]</sup> (figure 7).





**Figure 6.** A 29-year-old woman presented with abdominal pain. MRI demonstrated a large left adrenal mass and a lesion in the right hepatic lobe. (A) The concurrent I-131 MIBG scan of the anterior abdomen demonstrated increased tracer accumulation in the primary mass and the right hepatic lobe. Pathology revealed pheochromocytoma. (B) Follow-up CT scan, acquired 7 months after left adrenalectomy and right segmental hepatic resection, demonstrated a mass in the left adrenal bed (arrow). (C) A subsequent repeat I-131 MIBG scan demonstrated isolated tracer accumulation (arrow), consistent with post-surgical residual or recurrent pheochromocytoma.





**Figure 7.** A 71-year-old woman with a history of small bowel carcinoid and liver metastases. (A) The 48-hour standard I-131 MIBG scan demonstrated scattered foci of increased tracer accumulation in the abdomen (predominantly right lower quadrant) and in the liver. (B) Improved image quality and more confident localization of metastases in the abdomen and liver are demonstrated on a repeat whole-body scan acquired 72 hours after therapeutic administration of 410 mCi of I-131 MIBG.

## Tables

**Table 1. Sensitivity of Scintigraphy in Selected Tumors**

Type	I-131 MIBG	In-111 Octreoscan
Pheochromocytoma	85%	87%
Carcinoid (overall)	59%	95%

□ Midgut origin	67%	-
□ Increased serum serotonin	80%	-
Neuroblastoma	91%	89%

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