Somatostatin Receptor Imaging of Neuroendocrine Tumors With Indium-111 Pentetreotide (OctreoScan)

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Somatostatin, a naturally occurring 14-amino acid peptide, can be thought of as an anti-growth hormone and functional down-regulator of sensitive tissue. Most neuroendocrine tumors seem to possess somatostatin receptors in sufficient abundance to allow successful scintigraphic imaging with radiolabeled somatostatin congeners. Several of these, including Indium-III-DTPA Pentetreotide (Octreoscan [Mallinckrodt Medical, St. Louis, MO]), which was approved for clinical use by the Food and Drug Administration in June 1994, have been of considerable value in scintigraphically identifying various neuroendocrine tumors. The Octreoscan compares favorably with other imaging modalities. The success of somatostatin receptor imaging in evaluating patients with suspected neuroendocrine tumors, including identifying otherwise radiographically occult lesions, has resulted in ranking somatostatin receptor imaging as the prime imaging procedure in patients with suspected neuroendocrine tumors at The Ohio State University.

THE NEUROENDOCRINE CELL CONCEPT

IN THE LATE 1960s, it was discovered that some cells of the gastrointestinal tract were derived from embryonic neural crest tissue and were related to neural crest tissue found elsewhere, such as the hypothalamus, pituitary, thyroid, and adrenal medulla (Fig 1). These cells had two features in common: the production of peptide hormones and the ability to synthesize amines from precursors. These related cells were originally known as APUD (amine precursor uptake and decarboxylation) cells. APUD cells produce peptides and amines that act as hormones or neurotransmitters. As it became clear that the characteristic amines and peptides associated with APUD cells were present both in the central nervous system and endocrine system, the term "neuroendocrine" replaced the term "APUD" for describing these cells.

SOMATOSTATIN

Peptide formation and secretion by many neuroendocrine cells is inhibited by somatostatin, a 14-amino acid peptide that can be thought of as an anti-growth hormone[1,2] (Fig 2A). Somatostatin was first isolated from hypothalamic extracts and shown to inhibit the release of growth hormone from the anterior pituitary by Brazeau, Guillemin, and Schally in 1973.[3,4] Subsequently, somatostatin was shown to inhibit the release of other anterior pituitary hormones including adrenocorticotrophic hormone (ACTH), prolactin (PRL), and thyroid-stimulating hormone (TSH).

Somatostatin also inhibits the release of several intestinal peptides such as insulin, glucagon, gastrin, motilin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), secretin, cholecystokinin, and gastrin releasing peptide (GRP).[1] GRP stimulates proliferation of normal and malignant intestinal epithelium and normal bronchial epithelial cells.[5] It is also an autocrine growth factor in small-cell lung carcinoma.[6]

In an excellent review of mechanisms of somatostatin influence on tumor growth, Lamberts et al describe somatostatin-mediated inhibition of epidermal growth factor (EGF).[7] Somatostatin inhibitor of EGF induced cell proliferation was originally demonstrated by Mascardo.[8] However, somatostatin does not seem to regulate or inhibit the release of all growth factors. As of yet, there is no evidence for somatostatin-mediated inhibition of nerve growth factor (NGF), platelet-derived growth factor (PDGF), or hematopoietic growth factors such as erythropoietin, granulocyte colony-stimulating factor, or the interleukins.[4]

Somatostatin and its congeners can potentially exert antiproliferative effects on neuroendocrine tumors by several different mechanisms, including (1) the inhibition of regulatory peptide release from pituitary, intestinal, pancre-

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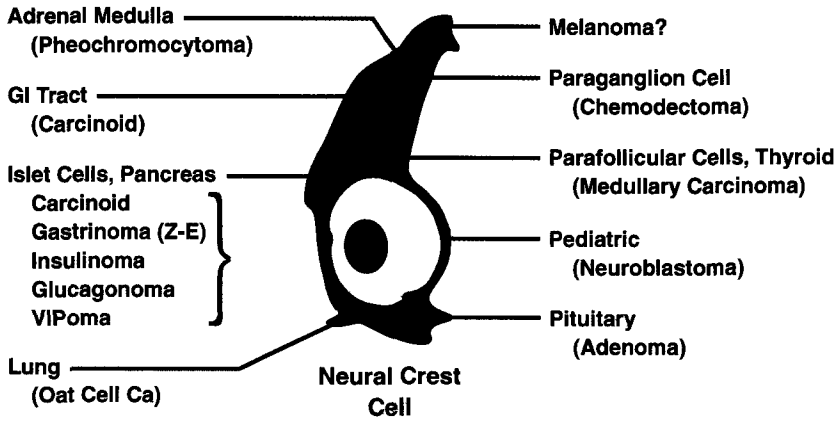


Fig 1. Tissues of neural crest origin and associated neoplasms.

atic, and other somatostatin-sensitive endocrine tissues; and (2) direct antagonism of growth-factor effects on tumor cells.[4,7] Somatostatin seems to inhibit several different signal transduction pathways, including the formation of cyclic adenosine monophosphate (cAMP),[9] diacyl glycerol (DAG),[10] ion channel movements of calcium (Ca^{2+})[11] and potassium (K^+),[12] and protein phosphorylation (tyrosine phosphatase activation).[13] As would be expected based on multiple mechanisms of action, there are several subtypes of somatostatin receptor.[14,15]

Table 1 lists the incidence of somatostatin receptors in various neuroendocrine tumors. Theoretically, somatostatin can be administered as a medication to control the release of biologically active peptides when they are being produced in excess by receptor-bearing neuroendocrine tumors. The antiproliferative effects of somatostatin may also assist in controlling and even reducing tumor size. However, somatostatin must be infused intravenously and has an exceedingly short biological half-life (plasma half-life of 2 to 4 minutes). In an attempt to increase the therapeutic effectiveness of somatostatin, a number of derivatives of this naturally occurring peptide have been made. One of these congeners has a sequence of eight amino acids and was given the name "octreotide"[2,14] (Fig 2B). The sequence and loop structure of the four amino acids that bind to receptors were retained, whereas the remainder of the molecule was altered to inhibit breakdown in the circulation; thus octreotide has a considerably longer plasma half-life than native somatostatin and is more potent. This synthetic somatostatin analog, octreotide, is currently marketed as Sandostatin (Sandoz, Basel, Switzerland).

The next development was a study of the feasibility of nuclear imaging with ^{123}I-labeled

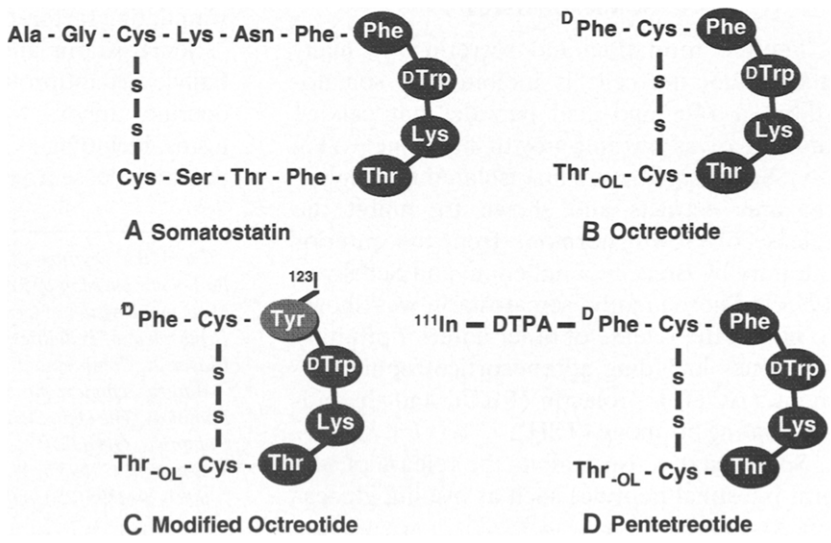


Fig 2. Structure of (A) somatostatin, (B) octreotide (Sandostatin), (C) I-123 Tyr Octreotide, and (D) OctreoScan.

Table 1. Incidence of Somatostatin Receptors in Neuroendocrine Tumors

Tumor Type	In Vivo	Scintigraphy (%)
Gastrinoma	12/12	100
Insulinoma	14/23	51
Carcinoid	69/72	96
Small-cell lung cancer	34/34	100
Paraganglioma	33/33	100
Glucagonoma	3/3	100
Neuroblastoma	8/9	89
Pheochromocytoma	12/14	86
Pituitary tumors	21/28	75
Medullary thyroid carcinoma	20/28	71
Unclassified APUDoma	16/18	89

Data from Krenning EP, et al: Eur J Nucl Med 20:716–731, 1993.

octreotide.[16,17] To radioiodinate the peptide, the third amino acid was changed from phenylalanine to tyrosine (Fig 2C). ^{123}I-labeled TYR-3 octreotide produced encouraging tumor-imaging studies. However, this compound is rapidly cleared by the liver, excreted into the hepatobiliary system and the intestines, where it interferes with images of the abdomen and pelvis. Delayed images were also less than ideal with the short 13-hour half-life of ^{123}I.

These deficiencies were corrected by the development of indium-111–labeled octreotide introduced into the United States by Mallinckrodt Medical Inc. (St. Louis, MO) with the trade name OctreoScan (Indium In-111 Pentetreotide)[16-18] (Fig 2D). DTPA placed on the *N*-terminus of the D-phenylalanine moiety at one end of the peptide allows labeling with indium-111 using a commercially available kit. This new radiopharmaceutical has been shown to successfully localize a wide variety of somatostatin receptor–positive tumors including carcinoid, islet cell tumors, gastrinoma, motiloma, pheochromocytoma, small-cell lung carcinoma, medullary thyroid carcinoma, neuroblastoma, paraganglioma, glucagonoma, pituitary adenoma, meningioma, vipoma, and insulinoma.[16,18] This agent is currently undergoing clinical studies to determine its usefulness for imaging other tumors such as breast cancer and lymphoma.

RADIOPHARMACEUTICAL

Indium-111 is a proton-rich nuclide that decays by electron capture to cadmium-111 with a physical half-life of 2.83 days. The principal photons useful for detection and imaging studies are a 171.3-keV gamma radiograph with an abundance of 90.4% and a 245.4-keV gamma ray with an abundance of 94.0% per disintegration.[19]

After injection, OctreoScan is rapidly cleared by the kidneys. Only approximately 2% of the injected dose undergoes hepatobiliary excretion. Within 10 minutes after administration, approximately 33% of the dose remains in circulation. At 4 hours postinjection only 10% of the injected dose is still in circulation, and at 24 hours postinjection less than 1% of the dose remains circulating. This rapid clearance serves to enhance the tumor-to-background ratio, and the relatively low-hepatobiliary clearance facilitates abdominal imaging. Analyses of urine and blood samples have shown that OctreoScan is primarily excreted intact with a biological half-life of 6 hours.

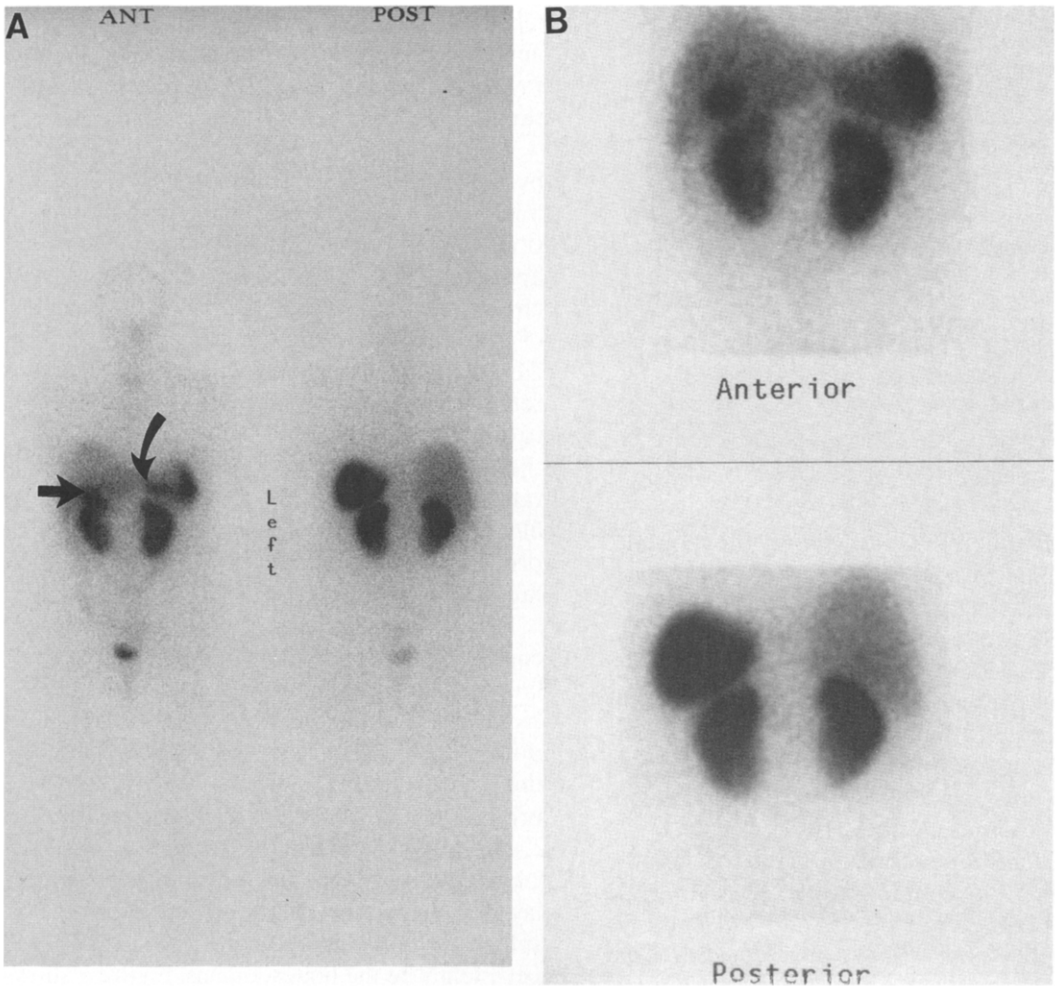
In normal subjects, OctreoScan uptake occurs in the thyroid, liver, gallbladder, spleen, kidneys, and bladder. With the exception of the kidneys and spleen, this physiological uptake is diffuse and generally does not interfere with the imaging of receptor-bearing tumors in these organs. Although OctreoScan is primarily excreted by the kidneys, the kidneys retain sufficient uptake to remain quite hot even on delayed imaging. Retention of octreotide in the spleen is also high. These two organs will persistently be the hottest organs. Figure 3 shows a normal study including whole-body images, spot images, and upper abdomen tomography.

DOSIMETRY

As would be expected from the previous discussion, the largest radiation burden from OctreoScan is delivered to the spleen and kidneys. A standard 6-mCi (222 mGy) dose delivers approximately 14.5 rads (147.7 mGy) to the spleen and 10.8 rads (108.3 mGy) to the kidneys. The bladder wall receives approximately 6 rads (60.5 mGy) and the liver approximately 2.5 rads (24.3 mGy). The other organs receive considerably less, including just under 1.0 rad (9.8 mGy) to the ovaries and approximately 0.6 rads (5.8 mGy) to the testes and the red bone marrow (Table 2).[19]

PATIENT PREPARATION

There are no diet restrictions for an OctreoScan imaging study. Patients may take any



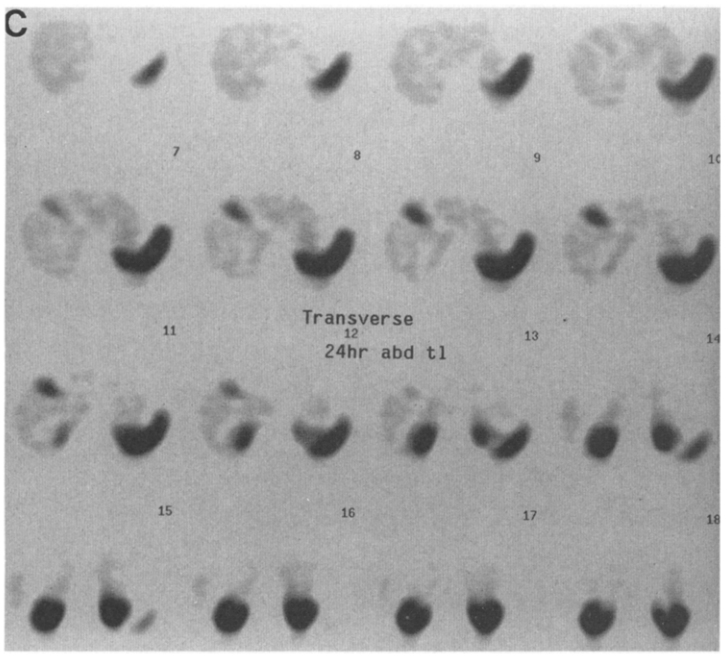


Fig 3. Normal OctreoScan image set. (A) Anterior and posterior whole-body images. Note faint uptake in the anterior pituitary and thyroid on the anterior image. The liver, spleen, kidneys, and urinary bladder are readily identifiable. The short horizontal arrow denotes the gallbladder. The curved arrow denotes a medial projection of the spleen. This relationship is clarified by the upper abdomen tomogram. Note the faint residual activity in the colon. (B) Anterior and posterior spot films of the upper abdomen. (C) Images selected from the transverse reconstruction of the 24-hour upper-abdomen SPECT study show spleen, gallbladder, both kidneys, and the medial projection of the spleen.

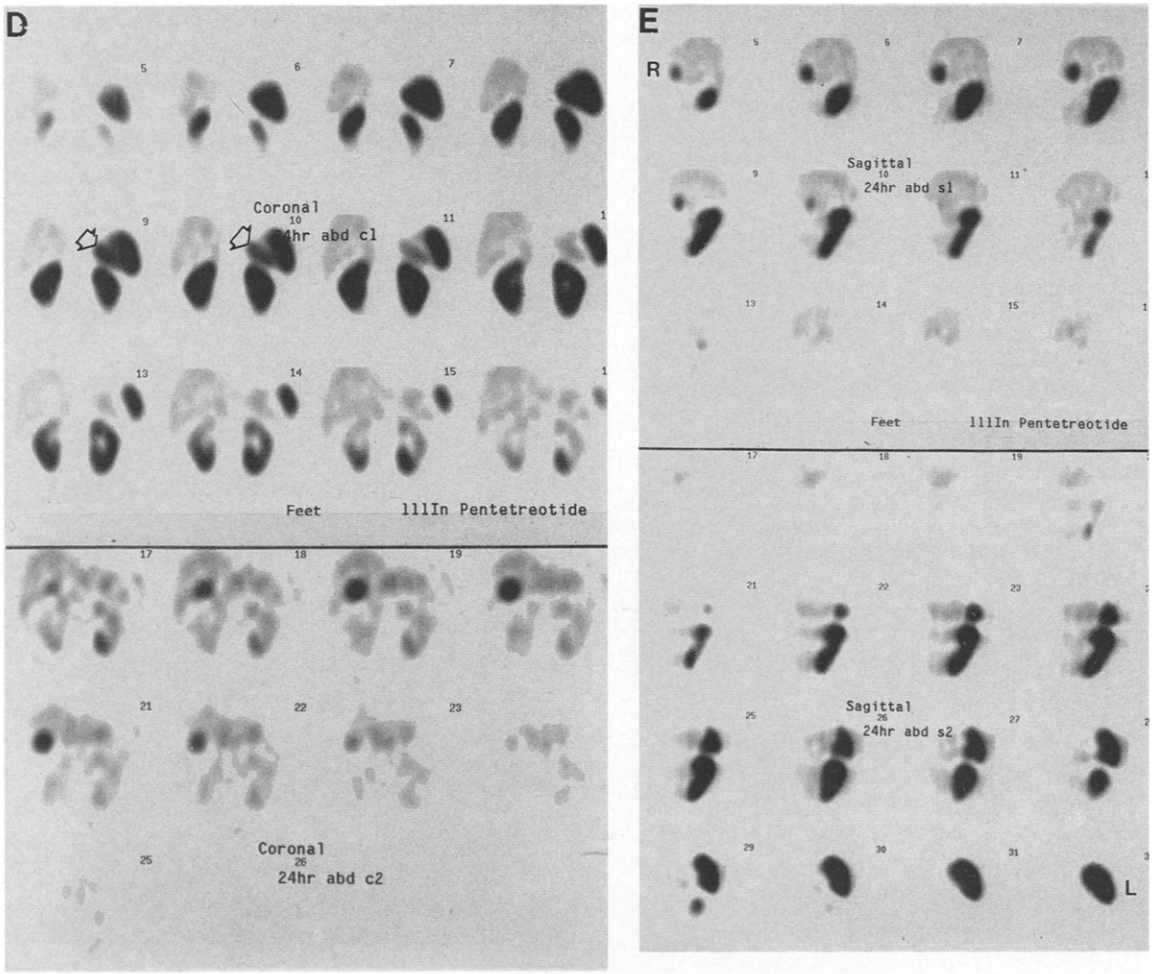


Fig 3 (Cont'd). (D) Images from the coronal SPECT reconstruction image of the upper abdomen from posterior (5) to anterior (23) show the liver, spleen, kidneys, and gallbladder. The open arrowhead indicates the medial projection of spleen. (E) Images from the sagittal SPECT reconstruction from right (5) to left (32) show the position of the gallbladder, right kidney, left kidney, and spleen.

medication except Sandostatin. Patients taking Sandostatin medication are required to discontinue Sandostatin 72 hours before the administration of OctreoScan. To enhance renal clearance, patients are hydrated with two 8-oz glasses of water before injection. The recommended dose is 6 mCi (222 MBq) of Indium In-111 Pentetreotide IV. All patients are asked to use a laxative, generally consisting of four Ducolax (bisacodyl) tablets, 5 mg each, one 10-fluid ounce bottle of Citroma (magnesium citrate solution), and three packets of Metamucil (natural psyllium fiber).

IMAGING PROTOCOL

4-Hour Images

The original imaging protocol, provided by the sponsor as part of a multicenter trial, called for images 4 hours postinfusion. Our observation is that findings shown by these early images are also apparent on later images. If 4-hour images are made, the imaging procedure consists of digital planar images with 600 seconds per view and a 256-word matrix. The views obtained are anterior and posterior abdomen (dome of liver at the top of the field of view), anterior and posterior pelvis (the lower tip of liver at the top of the field of view), and/or digital whole-body images with anterior and posterior projections using a 256-word matrix.

24–Hour Images

We obtain high-resolution anterior and posterior whole-body images using a 256-word ma-

Table 2. Estimated Absorbed Radiation Doses After Intravenous Administration of Indium In-111 Pentetreotide

Organ	rads (mGy)/6 mCi (222 MBq)
Kidneys	10.83 (108.3)
Liver	2.43 (24.3)
Spleen	14.77 (147.7)
Uterus	1.27 (12.7)
Ovaries	0.98 (9.8)
Testes	0.58 (5.8)
Red marrow	0.69 (6.9)
Urinary bladder wall	6.05 (60.5)
Stomach wall	1.13 (11.3)
Small intestine	0.96 (9.6)
Upper large intestine wall	1.16 (11.6)
Lower large intestine wall	1.55 (15.5)
Adrenals	1.51 (15.1)
Thyroid	1.49 (14.9)
Effective dose equivalent	2.61 (26.1)

Data from OctreoScan Kit for the preparation of Indium In-111 Pentetreotide Package Insert, Mallinckrodt Medical Inc (St. Louis, MO).

trix, medium energy general purpose (MEGP) collimator, and a scan speed of 8 cm/min. Digital planar spot images are also made at 600 seconds per view using a 256-word matrix and a MEGP collimator. The views obtained are anterior and posterior thorax (dome of liver at bottom of field of view), anterior and posterior abdomen (dome of liver at top of field of view), and anterior and posterior pelvis (lower tip of liver at top of field of view). We do not routinely make spot images of the head unless there is a clinical reason to suspect pathology or if the whole-body image suggested possible abnormality.

We obtain SPECT images of the upper abdomen in all patients. We feel that these images are essential to evaluate the region of the pancreas and duodenum (Fig 4) because of the

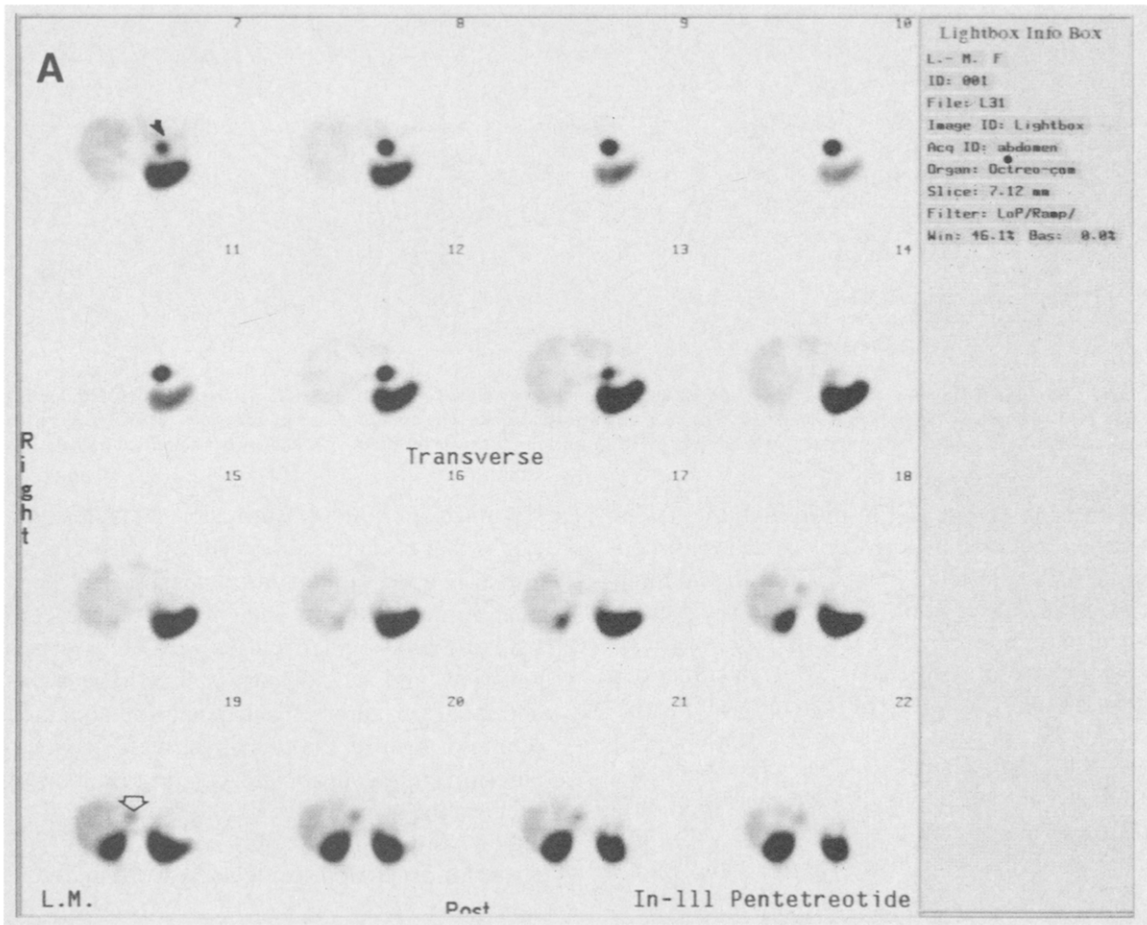


Fig 4. Transverse (A) and coronal (B) reconstruction of the upper abdomen in a patient with Zollinger-Ellison syndrome. A large gastrinoma (black arrowheads) in the tail of the pancreas was also visible on planar images (not shown); however, the small gastrinoma (open arrowhead) in head of the pancreas was only shown on the SPECT study. A CT examination of the abdomen failed to detect either lesion.

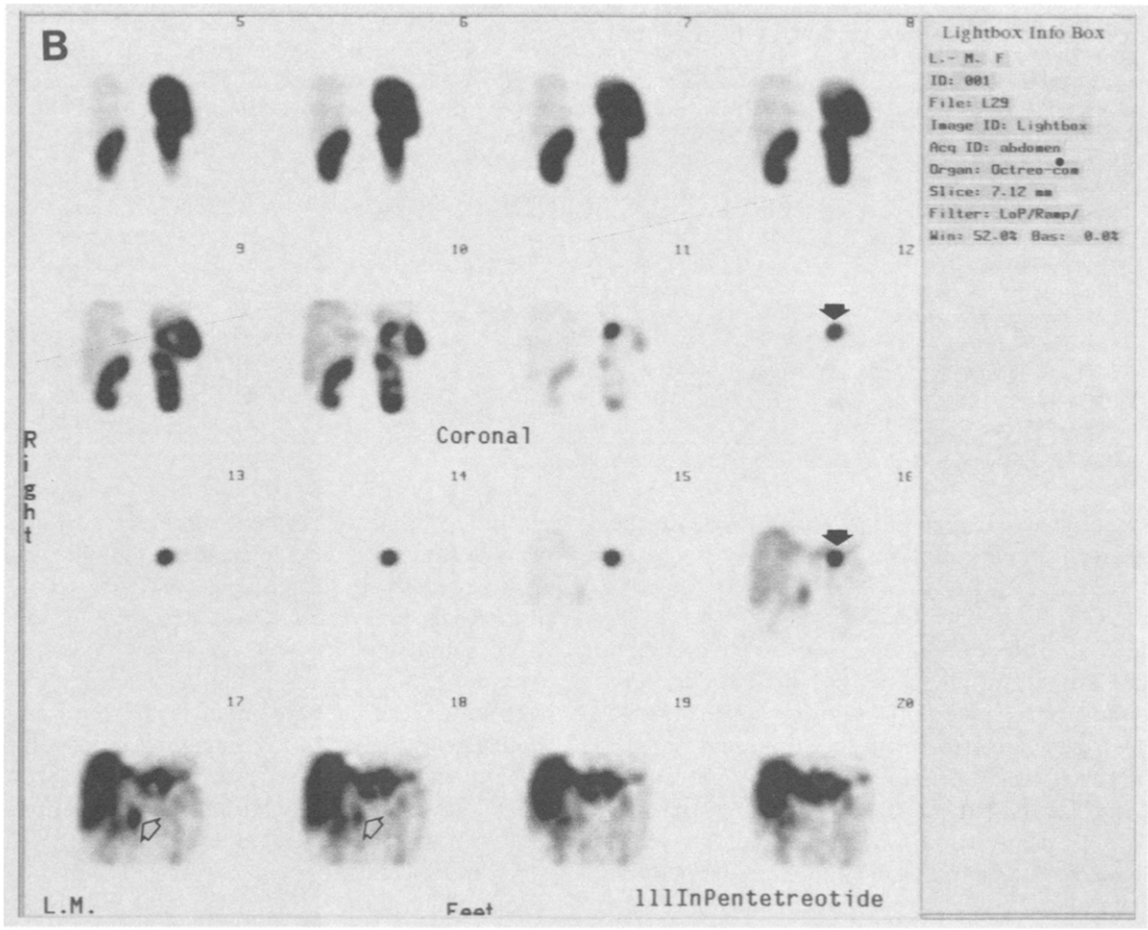


Fig 4 (Cont'd).

high competing signal from the kidneys, spleen, and often the gallbladder. A multi-head camera is preferable because it allows reduction in imaging time. We generally perform our studies on a dual-head camera using MEGP collimation, 128 × 128 word matrix, 60 steps and 40 to 45 seconds per step. This protocol applies to the thorax, abdomen, or pelvis. When a three-head camera is used, we image 40 steps so in each instance 120 data sets are collected for reconstruction.

Our three-dimensional postfilter rule of thumb is as follows: (1) if lesions are present on planar images, a Wiener filter is used; (2) if no lesion is identified on the planar images, or the study is a low-count study (ie, 48-hour thorax SPECT), a low pass filter may be better. There is no perfect filter; it seems to be very patient-dependent. We use attenuation correction unless the study is very low-count.

48–Hour Images

These are done as needed, per review by physician, but are not standard. Forty-eight–hour images may be made, for example, when there is a question concerning residual bowel or gallbladder activity, versus tumor, or to further evaluate a questionable abnormality shown on 24-hour images. In cases in which more areas must be evaluated than can be tolerably imaged at 24 hours, a part of the imaging is continued at 48 hours. When tomograms are obtained at 48 hours, the thorax is imaged at 50 to 55 seconds per step and the abdomen and pelvis at 45 to 50 seconds per step.

The imaging requirements are not technically difficult, but are demanding in terms of time and patient cooperation. We have found that patients suspected of having neuroendocrine pathology tend to be cooperative and motivated

Table 3. Multicenter Results

Tumor Type	True-Positive	True-Negative	False-Positive	False-Negative	Unconfirmed-Positive	Proportion Consistent (%)
Carcinoid	185	5	0	47	41	190/237 (80)
Gastrinoma	38	2	0	2	8	40/42 (95)
Glucagonoma	8	0	0	3	1	8/11 (73)
Insulinoma	4	0	1	8	1	4/13 (31)
Paraganglioma	6	0	0	1	2	6/7 (86)
Medullary thyroid carcinoma	10	2	0	10	4	12/22 (54)
Pituitary adenoma	18	6	0	6	0	24/30 (80)
Small-cell lung carcinoma	2	0	0	0	1	2/2 (100)
Vipoma	6	0	0	1	1	6/7 (86)
Pheochromocytoma	8	1	0	0	0	9/9 (100)
Misc. neuroendocrine tumors	68	3	0	16	9	71/87 (82)
NE tumor unproven	1	18	1	0	0	19/20 (95)
All types	363	38	3	104	70	401/508 (79)

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to do whatever may be necessary to locate the source of their symptoms.

IMAGING RESULTS

The results of a nine-center study conducted in Europe involving a total of 365 patients with either proven or high clinical suspicions of gastro-entero-pancreatic-neuroendocrine tumors are listed in Table 3.[20] Seventy percent of the patients had no prior history of octreotide therapy. Octreotide was discontinued 12 to 72 hours before OctreoScan administration in those patients who were receiving medication. The data compare OctreoScan localizations with lesions identified by other imaging modalities, including computed tomography, ultrasound, magnetic resonance imaging, angiography, and/or biopsy. True-positives were lesions detected both by OctreoScan imaging and by one of these other means. True-negatives had no evidence of neuroendocrine tumor with either OctreoScan or other methods. A false-negative was a lesion detected by conventional methods but not by OctreoScan imaging. False-positives were lesions detected by OctreoScan imaging that were not confirmed by biopsy. An unconfirmed-positive was a lesion detected by OctreoScan imaging for which no follow-up biopsy was performed. Overall, the results with OctreoScan were in agreement with those obtained by other methods, including biopsy, for 79% of tumor locations (401/508). OctreoScan detected an additional 110 tumor localizations not seen with conventional methods. Of the 40 that underwent biopsy, 37 were subsequently confirmed as tumors (that is, true-positives). Three localizations were subsequently determined to be false-positives, and the remaining 70 localizations are unconfirmed. Overall, OctreoScan yielded information about unknown tumor localizations in 28% of patients, which is remarkable because all of these patients were thoroughly evaluated before entering this study.

King et al described a retrospective review of 24 patients suspected of having neuroendocrine tumor.[21] Ten of these were studied with iodine

Table 4. Clinical OctreoScan® Studies at the Ohio State University

Tumor	Total Number	Octreoscan Only	Octreoscan & Pathology	Octreoscan & CT	CT Only	Octreoscan & CT & Pathology
Gastrinoma	22	4	5			9
Carcinoid	38	11	2	8	1	5
Neuroblastoma	1					1
VIPoma	2	1				1
Medullary thyroid	10	2	1	4		
Insulinoma	4	1				3
Glucoganoma	4		3			1
Non-Small cell lung	4			1		1
Pheochromocytoma	1					1
Other	6	2		1		2

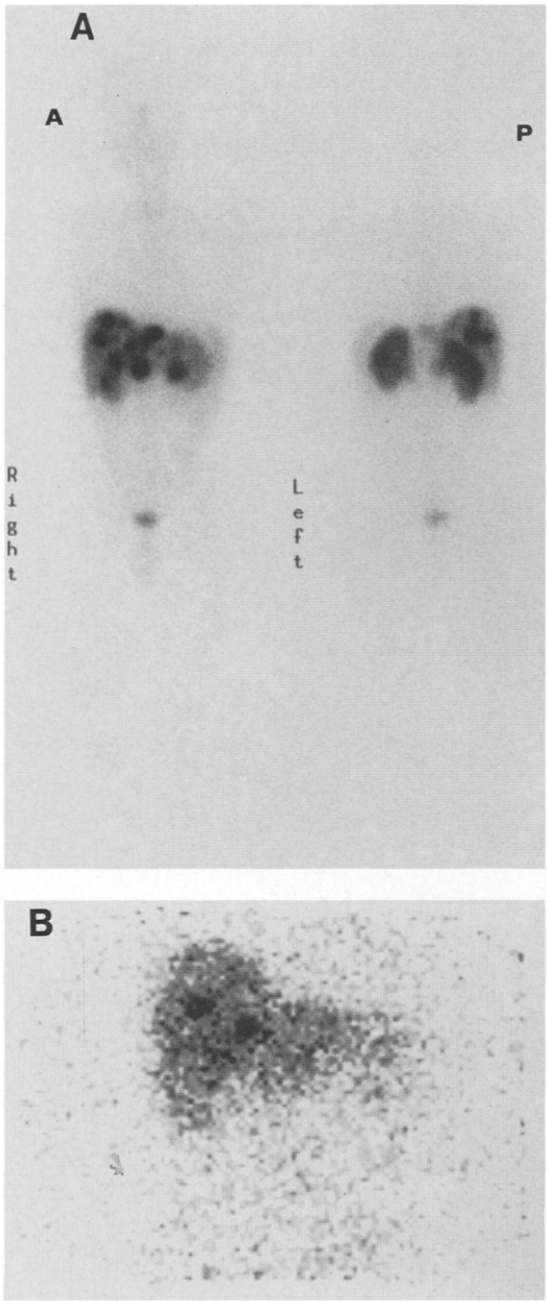

Fig 5. (A) Anterior (A) and posterior (P) whole-body images of a patient with metastatic carcinoid tumor show multiple discrete tumor lesions. (B) An anterior abdomen spot film made 10 days after the administration of OctreoScan. Between the time of (A) and (B), the patient underwent resection of the liver lesions. This image shows persistent OctreoScan uptake by somatostatin receptors on two liver lesions that were not resected.

123-try-octreotide and 14 were studied with OctreoScan. All of the OctreoScan studies used SPECT imaging, and all of the ^{123}I octreotide studies used SPECT imaging if there was no obvious lesion shown on planar imaging. All patients also had computed tomography (CT) and the nuclear imaging results are compared with the CT scans. Twenty of the 24 patients had neuroendocrine tumors with a total of 45 individual lesions. In their series, CT detected 42 tumors, whereas the sandostatin-receptor imaging detected only 31 lesions. Three lesions missed by CT were detected by scintigraphy, and there were 6 false-positive CT lesions. In 4 patients, no lesions were found by either modality, and subsequent evaluation and clinical follow-up have shown no evidence of tumor. They concluded that CT scanning was more sensitive than somatostatin-receptor scintigraphy, but expressed their opinion that both modalities were complimentary and that scintigraphy was especially useful in patients with disseminated pathology, equivocal CT lesions, or negative CT scan

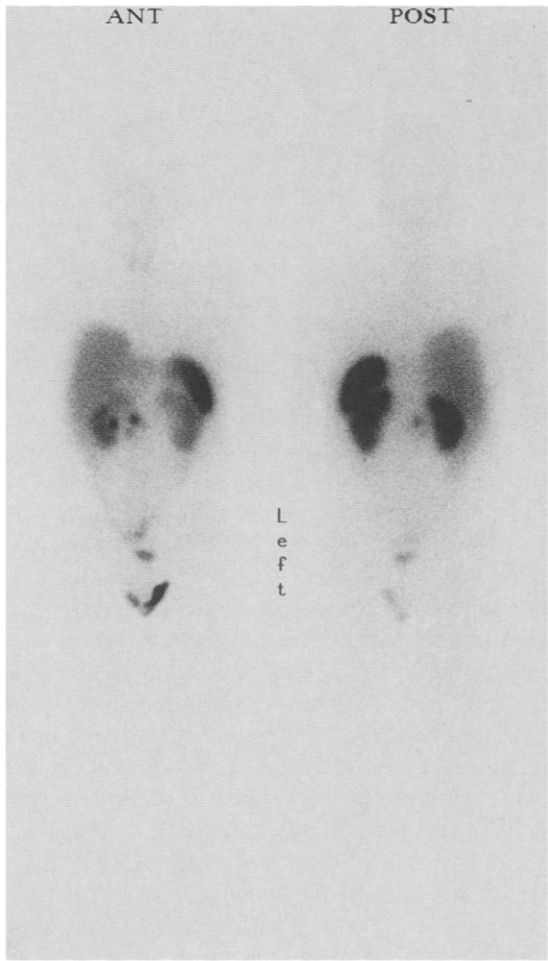

Fig 6. Anterior and posterior whole-body images of a patient with two gastrinomas in the head of the pancreas.

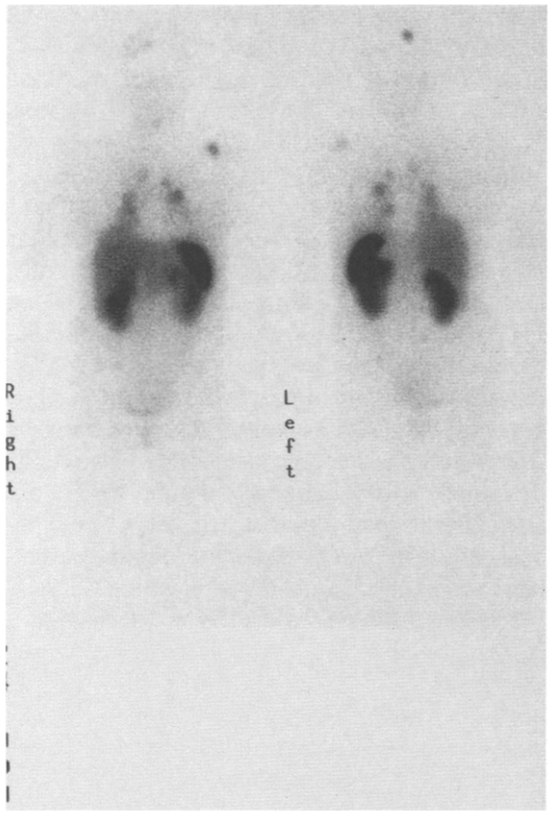

Fig 7. Anterior and posterior whole-body images of a patient with extensive metastatic medullary thyroid cancer.

results and a strong clinical suspicion of neuroendocrine tumor.

Our results at the Ohio State University are listed in Table 4. The distributions of lesions and the overall success is quite similar to the European data. These data are remarkable for the number of surgically confirmed localizations and for the fact that there are more incidences of positive OctreoScan/negative CT results than negative OctreoScan/positive CT results. The results have been such that our endocrine surgeons now strongly support somatostatin receptor imaging as the first imaging procedure when a neuroendocrine tumor is suspected. We have been impressed with the persistent adherence of OctreoScan to somatostatin receptors. We have re-imaged patients more than a week after administration of OctreoScan on several occasions and found that lesions are still identifiable. Figure 5A shows an example from a patient with extensive metastatic carcinoid to the liver. Multiple discrete lesions are identifiable. The patient was re-imaged postoperatively without additional OctreoScan 10 days after a "berry picking" procedure to remove the liver metastasis. Two of the lesions were not excised at surgery, and these two lesions were still clearly identifiable (Fig 5B).

CONCLUSION

Indium In-111 Pentetreotide (OctreoScan), a relatively new radiopharmaceutical, has shown considerable success in the visualization of vari-

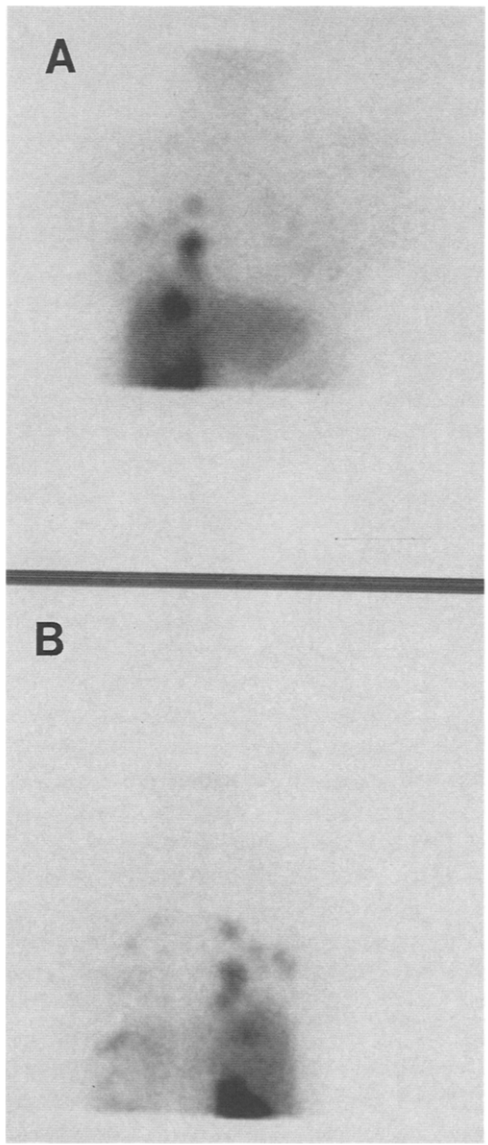

Fig 8. Anterior (A) and posterior (B) images of a patient with metastatic pheochromocytoma.

ous somatostatin receptor-positive neuroendocrine tumors (Figs 6 through 8). The sensitivity of scintigraphy is high for localizing neuroendocrine tumors, except in the case of insulinomas. In our institution Indium In-111 Pentetreotide scintigraphy is recommended as the first localization technique for neuroendocrine tumors. The whole-body coverage, relatively easy interpretation, and noninvasive nature of the test render this a logical choice.

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REFERENCES

1. Reichlin S: Somatostatin: Historical aspects. Scand J Gastroenterol 21:1-10, 1986

2. Kvols LK: Somatostatin-receptor imaging of human malignancies: A new era in localization, staging, and treatment of tumors. Gastroenterology 106:1909-1914, 1993

3. Brazeau P, Vale W, Burgus R, et al: Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 179:77-79, 1973

4. O'Dorisio MS, O'Dorisio TM: Neural crest tumors: Rationale for somatostatin and its analogs in diagnosis and therapy, in Mazzaferri EL, Samaan NA (eds): Endocrine Tumors (ed 1). Boston, MA, Blackwell, 1993, pp 533-540

5. Wiley JC, Lechner JG, Harris CC: Bombesin and the C-terminal tetradecapeptide of gastrin releasing peptide are growth factors for normal human bronchial epithelial cells. Exp Cell Res 153:245-248, 1984

6. Cuttitta F, Carney DN, Mulshine J, et al: Bombesin-like peptides can function as autocrine growth factors in human small-cell lung cancer. Nature 316:823-826, 1985

7. Lamberts WJ, Krenning EP, Reubi JC, et al: The role of somatostatin and its analogs in the diagnosis and treatment of tumors. Endocr Rev 12:450-482, 1991

8. Mascardo RN, Sherline P: Somatostatin inhibits rapid centrosomal separation and cell proliferation induced by epidermal growth factor. Endocrinology 111:1394-1396, 1982

9. Yajima Y, Akita Y, Saito T: Pertussis toxin blocks the inhibitory effects of somatostatin on cAMP-independent thyrotropin releasing hormone-stimulated prolactin secretion of GH 3 cells. J Biol Chem 261:2684-2689, 1986

10. Chen F, O'Dorisio MS, Hermann GE, et al: Mechanism of action of long-acting analogs of somatostatin. Regul Pept 44:285-295, 1993

11. Hsu WH, Xiang H, Rajan AS: Somatostatin inhibits insulin secretion by a G-protein-mediated decrease in Ca^{2+} entry through voltage dependent Ca^{2+} channels in beta cell. J Biol Chem 266:837-843, 1991

12. Koch BD, Schonbrunn A: Characterization of the cyclic AMP-independent actions of somatostatin in GH cells II: An increase in postassium conductance initiates somatostatin-induced inhibition of prolactin secretion. J Biol Chem 263:226-234, 1988

13. Liebow C, Lee MT, Schally A: Antitumor effects of somatostatin mediated by the stimulation of tyrosine phosphatase. Metabolism 39:163-166, 1990

14. O'Dorisio SM, Chen F, O'Dorisio TM, et al: Characterization of somatostatin receptors on human neuroblastoma tumors. Cell Growth Differ 1:1-8, 1994

15. Reubi JC, Krenning E, Lamberts SW, et al: In vitro detection of somatostatin receptors in human tumors. Digestion 54:76-83, 1993 (Suppl 1) (Review)

16. Krenning EP, Kwekkeboom DJ, Bakker WH, et al: Somatostatin recptor sctintigraphy with (^{111}IN-DTPA-D-Phe) and (^{123}I-Try$_3$)-octreotide: The Rotterdam experience with more than 1000 patients. Eur J Nucl Med 20:716-731, 1993

17. Krenning EP, Bakker WH, Breemon WAP, et al: Localisation of endocrine-related tumors with radioiodinated analogue of somatostatin. Lancet 1:242-244, 1989

18. Krenning EP, Bakker WH, Kooij PPM, et al: Somatostatin recptor scintigraphy with Indium-111-DTPA-D-Phe-1-Octreotide in man: Metabolism, dosimetry and comparison with Iodine-123 Try-3-Octreotide. J Nucl Med 33:652-658, 1992

19. Kit for preparation of Indium In-111 Pentetreotide, Mallinckrodt Medical Inc., St. Louis, MO

20. Data on file Mallinckrodt Medical: NDA submission for OctreoScan approval, submitted Nov 1992 and approved June 1994.

21. King CMP, Rezhek RH, Bomanji J, et al: Imaging neuroendocrine tumors with readiolabeled somatostatin analogues and x-ray computed tomography: A comparative study. Clin Radiol 48:386-397, 1993

22. Fischman AJ, Babich JW, Strauss HW: A ticket to ride: Peptide radiopharmaceuticals. J Nucl Med 34:2253-2263, 1993

23. Leitha T, Meghdadi S, Studnicka M, et al: The role of Iodine-123-Try-3-Octreotide scintigraphy in the staging of small-cell lung cancer. J Nucl Med 34:1297-1402, 1993

24. Kwekkeboom DJ, Urk H, Bernard KH, et al: Octreotide scintigraphy for the detection of paragangliomas. J Nucl Med 34:873-878, 1993

25. Lamberts SWJ, Krenning EP, Klijn JGM, et al: Clinical applications of somatostatin analogs. Trends in Endocrinol Metabolism 1:139-144, 1990