Society of Nuclear Medicine Procedure Guideline for Somatostatin Receptor Scintigraphy with In-111 Pentetreotide

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I. Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of somatostatin receptor scintigraphy with In-111 pentetreotide.

II. Background Information and Definitions

Indium-111 pentetreotide is a [In-111 DTPA-D-Phe] conjugate of octreotide, a somatostatin analog that binds to somatostatin receptors (predominantly somatostatin receptor subtypes sst2 and sst5). This octapeptide concentrates in neuroendrocrine and some non-neuroendrocrine tumors containing somatostatin receptors. Tumors that may be detected by somatostatin receptor scintigraphy with In-111 pentetreotide include, but are not limited to:

- adrenal medullary tumors (pheochromocytoma, neuroblastoma, ganglioneuroma)
- GEP (gastroenteropancreatic) tumors, e.g., gastrinoma, insulinoma, glucagonoma, VIPoma (vasoactive intestinal polypeptide secreting tumor) and non-functioning GEP tumors
- carcinoid tumors
- medullary thyroid carcinoma
- melanoma
- Merkel cell tumor of the skin
- paraganglioma
- pituitary adenomas
- small-cell lung carcinoma

Other tumors and disease processes may also be detected by In-111 pentetreotide scintigraphy and knowledge of the patient's history is thus important. These disorders may include, but are not limited to:

- astrocytomas
- benign and malignant bone tumors
- breast carcinoma
- differentiated thyroid carcinoma (papillary, follicular, Hürthle cell)
- lymphoma (Hodgkin's and non-Hodgkin's)
- meningioma
- non-small cell lung carcinoma
- prostate carcinoma
- renal cell carcinoma
- sarcomas
- autoimmune diseases (e.g., rheumatoid arthritis, Graves'disease, Graves' ophthalmopathy)
- bacterial pneumonia
- cerebrovascular accident
- fibrous dysplasia
- granulomas (e.g., tuberculosis, sarcoid)
- radiation pneumonitis

In addition to these tumors, normal organs, such as the pituitary, thyroid, spleen, liver, and renal parenchyma also demonstrate avidity for this tracer. The gallbladder, bowel, renal collecting systems, ureters and urinary bladder are seen as a result of clearance of In-111 pentetreotide.

III. Common Indications

A. Detection and localization of a variety of suspected neuroendocrine and some non-neuroendocrine tumors and their metastases (see Interpretation Criteria in section IV.H. below).
B. Staging patients with neuroendocrine tumors.
C. Determination of somatostatin-receptor status (patients with somatostatin receptor-positive tumors may be more likely to respond to octreotide therapy).
D. Follow-up of patients with known disease to evaluate potential recurrence.
E. Selection of patients with metastatic tumors for peptide receptor radionuclide therapy (PRRT) and prediction of the effect of PRRT, where available.

IV. Procedure

A. Patient Preparation
   1. When appropriate, consideration should be given to discontinuing octreotide therapy for 24 hr prior to In-111 pentetreotide administration, with monitoring the patient for signs of withdrawal. See also Section K.2.a.
   2. To reduce the radiation exposure, patients should be well hydrated prior to and for at least one day after injection.
   3. The use of laxatives should be considered, especially when the abdomen is the area of interest. A mild oral laxative (e.g., bisacodyl or lactulose) may be administered in the evening prior to injection and in the evening following injection. The need for bowel preparation should be assessed on an individual basis and laxatives should not be used in patients with active diarrhea.

B. Information Pertinent to Performing the Procedure

   A relevant history of the type of suspected or known primary tumor, its hormonal activity, the results of other imaging studies (CT, MRI), laboratory results (tumor markers), history of recent surgery, chemotherapy, radiation therapy, and octreotide therapy should be obtained. History of cholecystectomy should also be noted.

C. Precautions
   1. In patients suspected of having insulinoma, an intravenous infusion of glucose should be available because of the potential for inducing severe hypoglycemia.
   2. In-111 pentetreotide should not be injected into I.V. lines for, or together with solutions for total parenteral nutrition.

D. Radiopharmaceutical

   In-111 pentetreotide is a [In-111 DTPA-D-Phe-] conjugate of octreotide, a long-acting somatostatin analog (OctreoScan®). The recommended administered activity is 222 MBq (6 mCi) in adults and 5 MBq / kg (0.14 mCi / kg) in children. The amount of pentetreotide injected is 10-20 mg; that dose is not expected to have a clinically significant pharmacologic effect (see section IV.C.1 above). In-111 pentetreotide is cleared rapidly from the blood (one-third of the injected dose remains in the blood pool at 10 min, 1% at 20 hr postinjection). Excretion is almost entirely via the kidneys (50% of the injected dose is recovered in the urine by 6 hr, 85% within 24 hr). Hepatobiliary excretion is only about 2% of the administered dose. It is not known whether In-111 pentetreotide is removed by dialysis.

E. Image Acquisition
   1. Patients should void prior to imaging.
   2. Images are acquired at 4 and 24 hr or 24 and 48 hr post injection. The 48 hr images may be needed when there is significant bowel activity at 24 hr, which may potentially obscure lesions. Four-hour images may be obtained to enable evaluation prior to appearance of activity in the gut, but since tumor-to-background ratio is lower at 4 hr than at 24 and 48 hr, some lesions may be missed at 4 hr.
   3. Planar images are acquired using a large-field-of-view gamma camera fitted with a medium-energy collimator. Symmetrical 20% energy windows are centered over both photo peaks of In-111 (173 and 247 keV) and the data from both windows are added. Planar localized images of the head, chest, abdomen, pelvis, and, if needed, the extremities can be acquired for 10–15 min per image, using a 512 x 512 word or 256 x 256 word matrix. Occasionally, images may be required in areas with low tracer activity. If this is the case, images should be acquired in a suitable byte mode acquisition matrix. For whole-body images using a dual-head camera, it is suggested that anterior and posterior images are acquired into 1024 x 512 word or 1024 x 256 word matrix for a minimum of 30 min (head to upper femurs) and longer for the entire body (e.g., a speed of 3 cm / min has been sug-

Radiation Dosimetry for Adults*

Radiopharmaceutical	Administered Activity MBq (mCi)	Organ Receiving the Largest Radiation Dose mGy/MBq (rad/mCi)	Effective Dose Equivalent mSv/MBq (rem/mCi)
In-111 pentetreotide	222 (6)	spleen 0.665 (2.46)	0.117 (0.433)

* from OctreoScan® package insert, Mallinckrodt Medical, Inc. 1995.

gested) in a single pass. Since cervical lymph node metastases may be missed on the whole body images, additional planar localized images of the head and neck, including lateral views, are suggested.

SPECT imaging of the appropriate regions, as indicated based upon the clinical history, should be performed preferably with a multi-detector gamma camera. Early and delayed SPECT may be helpful in distinguishing bowel activity from pathological lesions. If only one SPECT acquisition is obtained, acquisition at 24 hr is preferred because of higher target-to-background ratio.

Although imaging systems may vary, an example of potentially useful acquisition parameters for a multi-detector system are: 3° angular sampling, 128 x 128 matrix, 360° rotation, 20–30 sec per stop.

For more information see the *Society of Nuclear Medicine Procedure Guideline for General Imaging.*

F. Interventions
None

G. Processing
See the *Society of Nuclear Medicine Procedure Guideline for General Imaging.*

In general, SPECT raw data are pre-filtered using an appropriate low-pass filter, the order and frequency according to local preferences and software manufacturer recommendations. The data is then reconstructed using a ramp filter and attenuation correction. Newer systems may include iterative reconstruction algorithms, which may eliminate some of the artifacts seen with filtered backprojection in areas adjacent to intense tracer activity.

H. Interpretation Criteria
1. When possible, images should be evaluated in conjunction or fused with relevant anatomical images (e.g., CT, MRI).
2. The optimal time interval to localize tumors is at 24 hr postinjection or later. At 4 hr the background activity may be high. Nevertheless, early images may be important for comparison and evaluation of abdominal activity imaged at 24 hr.
3. Images are best viewed at the computer display with individualized physician-directed optimization of intensity and contrast. Three-dimensional rendering of the SPECT data and its review in cinematic display is encouraged.
4. Knowledge of normal tissue accumulation of In-111 pentetreotide is important for study interpretation. This radiotracer is seen in the pituitary, thyroid, liver, spleen, kidneys, bladder, and occasionally the gallbladder. Intestinal activity is usually not present at 4 hr, but may be present at 24 hr; 48 hr images may be necessary to clarify abdominal activity.
5. Islet cell tumors: peptide hormone-producing endocrine tumors of the pancreas and GI tract and their metastases, including gastrinomas, insulinomas, VIPomas (vasoactive intestinal polypeptide-secreting tumors), glucagonomas, as well as non-functioning islet cell tumors may be imaged with In-111 pentetreotide. The sensitivity for these lesions is 75–100% except for insulinoma, where it may be as low as 50–60%, due to the presence of different somatostatin receptor subtypes on this tumor.
6. Pheochromocytomas, neuroblastomas, and paragangliomas: the advantage of somatostatin receptor scintigraphy with In-111 pentetreotide is the ability to detect primary lesions and metastases in unexpected (extraadrenal) sites not investigated by CT or MRI. Tumors in the adrenal glands may be difficult to detect due to high renal activity; imaging with I-131 or I-123 meta-iodobenzylguanidine (MIBG) may be preferable for tumor localization in the adrenal area. The sensitivity of In-111 pentetreotide for these tumors is over 85%.
7. Medullary thyroid carcinoma: the sensitivity of In-111 pentetreotide scintigraphy may be lower than for other tumors (65–70%). Comparison with Tc-99m sulfur colloid scintigraphy for liver metastases or with I-123 scintigraphy for intrathyroidal tumors may increase the rate of lesion detection, especially when the uptake of In-111 pentetreotide in these organs is homogeneous.
8. Carcinoid: the overall sensitivity of In-111 pentetreotide scintigraphy is approximately 86–95%. For extrahepatic lesions, sensitivity for lesions over 1 cm in diameter may exceed 90%; however, hepatic lesions may be isointense. SPECT imaging of the liver is recommended even if the planar images appear normal.
9. Intracranial tumors: meningiomas are rich in somatostatin receptors and are therefore highly detectable. In-111 pentetreotide scintigraphy may be used for postoperative follow-up of this tumor. Grade I and II astrocytomas are also somatostatin receptor-positive, grade III astrocytomas may or may not be, while grade IV (glioblastoma multiforme) is typically somatostatin receptor-negative. Localization of In-111 pentetreotide in an astrocytoma also requires

that the blood-brain barrier be impaired.

10. Lung carcinoma: the sensitivity for primary sites of disease is reported to be 80–100% for small-cell lung cancer (SCLC), it may be lower for non-small cell lung cancer.

I. Reporting

In addition to the general information to be provided in each Nuclear Medicine report as recommended in the Society of Nuclear Medicine Guideline on General Imaging (section VI.D), it is suggested that the report contain the following information:

1. Indication: results of laboratory tests (e.g., neuroendrocrine tumor markers if applicable), or results of other imaging studies as well as other relevant history (known tumor and its type, recent radiation therapy, chemotherapy).
2. Relevant medications: e.g., octreotide therapy and when stopped, chemotherapy, laxatives, if given.
3. Procedure description: timing of imaging relative to radiopharmaceutical administration; areas imaged; whether SPECT was performed and if so, its timing and body areas included.
4. Study limitations: the referring physician may be reminded that some tumors may lack somatostatin receptors or the appropriate receptor subtypes and, therefore, may not be detected. The differential diagnosis should consider the many potential causes for a false-positive study, as listed in section IV.K1.

J. Quality Control

1. Prior to the administration of In-111 pentetreotide, the labeling yield of the radiopharmaceutical should be tested according to the manufacturer's instructions. The product should not be used if radiochemical purity is less than 90%.
2. The radiopharmaceutical should be used within 6 hr of preparation.
3. In-111 pentetreotide should be inspected visually prior to administration. Preparations containing particulate matter or color should not be administered.

K. Sources of Error

1. Potential causes for a false-positive interpretation:
   a. Accumulation of In-111 pentetreotide in the nasal and pulmonary hilar areas can be seen with respiratory infections.
   b. Diffuse pulmonary or pleural accumulation of In-111 pentetreotide can be observed following radiation therapy to the lung or bleomycin therapy.
   c. The tracer may accumulate at recent surgical and colostomy sites.
   d. Accumulation of the tracer in normal structures (pituitary, thyroid, liver, spleen, kidneys, bowel, gallbladder, ureters, bladder, stimulated adrenal glands) and in multiple disorders (some listed in Section II) must be kept in mind. Caution must be used to avoid interpreting physiologic gallbladder activity as hepatic metastasis.
2. Potential causes for a false-negative interpretation:
   a. Presence of unlabeled somatostatin, either as a result of octreotide therapy or due to production of somatostatin by the tumor itself may lower tumor detectability, however, there are also literature reports of improved tumor-to-background ratio following pretreatment with non-radioactive octreotide.
   b. Different somatostatin receptor subtypes have different affinities for the radioligand; variable tumor differentiation/receptor expression also influences tumor detectability. This is a consideration, especially with insulinomas and medullary thyroid carcinomas.
   c. Liver metastases of neuroendocrine tumors may appear isointense because of a similar degree of tracer accumulation by the normal liver. Correlation with anatomic imaging or subtraction scintigraphy with sulfur colloid may be considered.

V. Issues Requiring Further Clarification

A. Since In-111 pentetreotide elimination in patients with impaired renal function has not been studied, possible dosage adjustment in these patients needs to be clarified.

B. The role of In-111 pentetreotide scintigraphy in breast carcinoma, renal cell carcinoma, Hodgkin's and non-Hodgkin's lymphoma and other tumors (see section II.), as well as in the evaluation and management of some granulomatous and autoimmune processes (e.g. activity of sarcoidosis, response of Graves' ophthalmopathy to steroids, etc) is yet to be determined.

C. This procedure guideline only covers imaging with In-111 pentetreotide. Imaging with other somatostatin analogs (e.g., Tc-99m depreotide) is not a subject of this guideline.

VI. Concise Bibliography

Gibril F, Reynolds JC, Chen CC, et al. Specificity of so-

matostatin receptor scintigraphy: a prospective study and effects of false-positive localizations on management in patients with gastrinomas. *J Nucl Med* 1999;40:539-553

Gibril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. *Ann Intern Med* 1996;125:26–34.

Hochstenbag MM, Heidendal GAK, Wouters EFM, at al. In-111 octreotide imaging in staging of small cell lung cancer. *Clin Nucl Med* 1997;22:811–816.

Jamar F, Fiasse R, Leners N, et al: Somatostatin receptor imaging with indium-111 pentetreotide in gastroenteropancreatic neuroendocrine tumors: safety, efficacy and impact on patient management. *J Nucl Med* 1995; 36:542–549.

Klutmann S, Bohuslavizki KH, Brenner W, et al. Somatostatin receptor scintigraphy in postsurgical follow-up examinations of meningioma. *J Nucl Med* 1998;39:1913–1917.

Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [In-111-DTPA-d-Phe1] and [I-123-Tyr3]-octreotide: the Rotterdam experience with more than 1000 *patients*. Eur J Nucl Med 1993;20:716–731.

Krenning EP, Kwekkeboom DJ, Pauwels S, et al. Somatostatin receptor scintigraphy. *Nucl Med Annual* 1995;1–50.

Kwekkeboom DJ, Krenning EP, Kho GS, et al. Somatostatin receptor imaging in patients with sarcoidosis. *Eur J Nucl Med* 1998; 25:1284–1292.

Kwekkeboom DJ, Krenning EP: Radiolabeled somatostatin analog scintigraphy in oncology and immune diseases: an overview. *Eur J Radiol* 1997; 7:1103–1109.

Lebtahi R, Cadiot G, Sarda L, et al. Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. *J Nucl Med* 1997; 38:853–858.

OctreoScan® package insert, Mallinckrodt Medical Inc. Revised March 1995

Olsen JO, Pozderac RV, Hinkle G, et al. Somatostatin receptor imaging of neuroendrocrine tumors with indium-111 pentetreotide (OctreoScan). *Semin Nucl Med* 1995;25:251–261.

Reisinger I, Bohuslavitzki KH, Brenner W, et al. Somatostatin receptor scintigraphy in small-cell lung cancer: results of a multicenter study. *J Nucl Med* 1998; 39:224–227.

Schmidt M, Scheidhauer K, Luyken C, et al. Somatostatin receptor imaging in intracranial tumours. *Eur J Nucl Med* 1998;25:675–686.

VIII. Disclaimer

The Society of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high quality nuclear medicine procedures. These generic recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be quite different than the spectrum of patients seen in a more general practice setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, the resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.