

# The SNM Practice Guideline for Somatostatin Receptor Scintigraphy 2.0\*

Helena R. Balon<sup>1</sup>, Tracy L.Y. Brown<sup>2</sup>, Stanley J. Goldsmith<sup>3</sup>, Edward B. Silberstein<sup>4</sup>, Eric P. Krenning<sup>5</sup>, Otto Lang<sup>6</sup>, Gary Dillehay<sup>7</sup>, Jennifer Tarrance, CNMT<sup>1</sup>, Matt Johnson, CNMT<sup>1</sup>, and Michael G. Stabin<sup>8</sup>

<sup>1</sup>William Beaumont Hospital, Royal Oak, Michigan; <sup>2</sup>University of Arkansas for Medical Sciences, Little Rock, Arkansas; <sup>3</sup>New York Hospital–Cornell Medical, New York, New York; <sup>4</sup>University of Cincinnati Medical Center, Cincinnati, Ohio; <sup>5</sup>Erasmus University Medical Center, Rotterdam, The Netherlands; <sup>6</sup>3rd Medical School, Charles University, Prague, Czech Republic; <sup>7</sup>Northwestern University, Chicago, Illinois; and <sup>8</sup>Vanderbilt University Medical Center, Nashville, Tennessee

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These guidelines are an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the SNM cautions against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines.

The practice of medicine involves not only the science, but also the art, of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

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For correspondence or reprints contact: Helena Balon, William Beaumont Hospital, 3601 W. Thirteen Mile Rd., Royal Oak, MI 48703.  
E-mail: hbalon@beaumont.edu  
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## I. INTRODUCTION

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of somatostatin receptor scintigraphy (SRS) with  $^{111}\text{In}$ -pentetreotide. The European Association of Nuclear Medicine guideline on  $^{111}\text{In}$ -pentetreotide scintigraphy (1) was taken into consideration throughout this guideline. This guideline covers imaging with only  $^{111}\text{In}$ -pentetreotide. Imaging with other somatostatin analogs is not a subject of this guideline.

## II. GOALS

The goal of SRS is to detect and localize a variety of neuroendocrine tumors in patients often with elevated neuroendocrine tumor markers, as well as some nonneuroendocrine tumors. SRS may help in preoperative evaluation, staging, and restaging of these tumors.

## III. DEFINITIONS

$^{111}\text{In}$ -pentetreotide is an agent used primarily for scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.  $^{111}\text{In}$ -pentetreotide (OctreoScan; Covidien Inc.) is [ $^{111}\text{In}$ -diethylenetriaminepentaacetic acid-D-Phe]octreotide, a somatostatin analog that binds to somatostatin receptors on cell surfaces. This octapeptide binds to somatostatin receptor-rich normal tissues and concentrates in neuroendocrine tumors and some nonneuroendocrine tumors containing somatostatin receptors (predominantly somatostatin receptor subtypes 2 and 5). Disorders that may be detected by SRS with  $^{111}\text{In}$ -pentetreotide include, but are not limited to, the following:

### A. Tumors with High Expression of Somatostatin Receptors

1. Adrenal medullary tumors (pheochromocytoma, neuroblastoma, ganglioneuroma, paraganglioma)
2. Gastroenteropancreatic neuroendocrine tumors (formerly termed carcinoid, gastrinoma, glucagonoma, vasoactive intestinal polypeptide-secreting tumor, pancreatic polypeptide-secreting tumor, etc., or nonfunctioning gastroenteropancreatic tumors), more recently classified by the World Health Organization as low grade, intermediate grade and high grade (G1, G2, and G3)
3. Merkel cell tumor of the skin
4. Pituitary adenoma
5. Small-cell lung carcinoma

### B. Tumors with Low Expression of Somatostatin Receptors

1. Astrocytoma
2. Benign and malignant bone tumors
3. Breast carcinoma
4. Differentiated thyroid carcinoma (papillary, follicular, Hürthle cell)

5. Lymphoma (Hodgkin and non-Hodgkin)
6. Melanoma
7. Meningioma
8. Non-small cell lung carcinoma
9. Prostate carcinoma
10. Renal cell carcinoma
11. Sarcomas

### C. Tumors with Variable Expression of Somatostatin Receptors (Especially Somatostatin Receptor Subtype 2)

1. Insulinoma
2. Medullary thyroid carcinoma

### D. Nonneoplastic Processes

1. Autoimmune diseases (e.g., rheumatoid arthritis, Graves' disease, Graves' ophthalmopathy)
2. Bacterial pneumonia
3. Cerebrovascular accident
4. Fibrous dysplasia
5. Granulomatous diseases (e.g., tuberculosis, sarcoid)
6. Postradiation inflammation

Thus, knowledge of the patient's medical history is important. In addition to these pathologies, normal organs such as the pituitary, thyroid, spleen, liver, and renal parenchyma also demonstrate avidity for  $^{111}\text{In}$ -pentetreotide. The gallbladder, bowel, renal collecting systems, ureters, and urinary bladder are seen as a result of tracer clearance.

## IV. EXAMPLES OF CLINICAL AND RESEARCH INDICATIONS

SRS may be used clinically for the following:

- A. Detection and localization of suspected neuroendocrine and some nonneuroendocrine tumors and their metastases (2–11)
- B. Staging of patients with neuroendocrine tumors (7,12–17)
- C. Follow-up of patients with known disease to evaluate for progression or recurrence (restaging) (10,12,17–20)
- D. Determination of somatostatin-receptor status (patients with somatostatin receptor-positive tumors may be more likely to respond to peptide receptor radionuclide therapy) (21–24)
- E. Evaluation of acute inflammation in rheumatologic disorders (25–27)

Recommendation for appropriate use of SRS in the management of various neuroendocrine tumors and lung neuroendocrine tumors is addressed in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (17).

## V. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL (IN THE UNITED STATES)

Please see Section V of the SNM Procedure Guideline on General Imaging.

## VI. PROCEDURE/SPECIFICATIONS OF THE EXAMINATION

### A. Request

The request should be made by a qualified physician or other licensed health-care professional familiar with the patient's clinical history. A relevant history; the type of suspected or known primary tumor; its hormonal activity; the results of other imaging studies (CT, MRI, ultrasound); laboratory results (tumor markers); history of recent surgery; and history of chemotherapy, radiation therapy, or octreotide therapy should be obtained. History of cholecystectomy and splenectomy should also be noted.

### B. Patient Preparation and Precautions

When safe and appropriate, consideration should be given to discontinuing octreotide acetate therapy before  $^{111}\text{In}$ -pentetreotide administration in consultation with the referring clinician. The length of withdrawal will depend on the type (half-life) of the therapeutic agent; at least 1 d is recommended for standard agents and 4–6 wk for long-acting/slow-release formulations.

To minimize radiation exposure, patients should be well hydrated before and for at least 1 d after tracer injection. The use of  $^{111}\text{In}$ -pentetreotide in patients with impaired renal function should be considered, as the rate of tracer excretion may be much slower than that in patients with normal renal function.

While there is no definitive literature on the use of  $^{111}\text{In}$ -pentetreotide in patients on dialysis, interpretable images may be obtained after dialysis.

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 before 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 or in patients with insulinoma.

For patients with suspected insulinoma, there is some controversy as to whether they need special attention during pentetreotide injection. The pentetreotide package insert states: "Since pentetreotide is an analog of octreotide, an intravenous line is recommended in any patient suspected of having an insulinoma. An intravenous solution containing glucose should be administered just before and during administration of Indium In-111 pentetreotide." While there have been no reports of hypoglycemic reactions in patients with insulinoma, each site should consider this caution and establish a local policy accordingly (15).

$^{111}\text{In}$ -pentetreotide should not be injected into intravenous lines used for, or together with, solutions for total parenteral nutrition (15).

$^{111}\text{In}$ -pentetreotide is classified as category C for use in pregnant women.

### C. Radiopharmaceuticals

$^{111}\text{In}$ -pentetreotide is a standard somatostatin analog. The recommended administered activity is 222 MBq (6 mCi) in adults and 3 MBq/kg (0.08 mCi/kg) in children. Based on in vitro studies, the hormonal effect of pentetreotide is approximately 10% that of octreotide. The amount of pentetreotide injected per dose of OctreoScan is 10  $\mu\text{g}$ . This dose is not expected to have a clinically significant pharmacologic effect (except in insulinoma, see VI.B).

$^{111}\text{In}$ -pentetreotide is cleared rapidly from the blood pool (one third of the injected dose remains in the blood pool at 10 min, 1% at 20 h after injection). Excretion is almost entirely via the kidneys (50% of the injected dose is recovered in the urine by 6 h, 85% within 24 h). Hepatobiliary excretion represents about 2% of the administered dose. The biologic half-life is 6 h. Adjustment of administered activity in patients with decreased renal function has not been studied.

### D. Protocol/Image Acquisition/Processing

Patients should void before imaging.

#### 1. Imaging protocol

Images are routinely acquired at 24 h. Four-hour and 48-h postinjection imaging is optional. The delayed images may be needed to allow clearance of significant bowel activity. Four-hour images may be obtained to enable evaluation before the appearance of activity in the gut, but since tumor-to-background ratio is lower at 4 h than at 24 and 48 h, some lesions may be missed at 4 h. SPECT (or SPECT/CT if available) imaging is preferably performed at 24 h after injection because of the higher target-to-background ratio at that time. Early and delayed SPECT may be helpful in distinguishing physiologic bowel activity from pathologic lesions.

#### 2. Image Acquisition

Planar images are acquired using a large-field-of-view  $\gamma$ -camera fitted with a medium-energy collimator. Symmetric 20% energy windows are centered over both photopeaks of  $^{111}\text{In}$  (173 and 247 keV), and the data are summed. Planar localized images of the head, chest, abdomen, pelvis, and, if needed, extremities can be acquired for 10–15 min per image, using a  $512 \times 512$  or  $256 \times 256$  matrix.

For whole-body images using a dual-head camera, it is suggested that anterior and posterior images are acquired into  $2,048 \times 512$  or  $1,024 \times 256$  matrices in a single pass at a speed that balances information density with practicability and patient comfort. Since cervical lymph node metastases may be missed on whole-body images, it is suggested that additional planar localized images of the head and neck, including lateral views, are obtained.

SPECT imaging of the appropriate regions, as indicated based on the clinical history or the planar images, is strongly recommended. It should be performed with a multidetector  $\gamma$ -camera when possible. Although imaging systems may

vary, an example of potentially useful acquisition parameters for a multidetector system is 3° angular sampling, 128 × 128 matrix, 360° rotation, and 20–30 s per stop.

SPECT/CT imaging may help localize foci of abnormal tracer accumulation more accurately than planar imaging or SPECT alone and should be considered whenever indicated and available (28–30). The patient's history, planar images, and other prior imaging studies should be reviewed to determine which body areas may benefit from using SPECT/CT. However, to limit the radiation dose to the patient, CT performed as part of hybrid SPECT/CT should be used judiciously.

An example of potentially useful CT acquisition parameters for attenuation correction/anatomic localization performed as part of a hybrid SPECT/CT acquisition could include a 5.0-mm slice thickness with a 2.5-mm collimation for attenuation correction.

### 3. Image processing

Iterative reconstruction with ordered-subsets expectation maximization is the recommended reconstruction algorithm, as it may eliminate some of the artifacts seen with filtered backprojection in areas near intense tracer activity. Specific parameters depend on vendor recommendations and local preferences.

On completion, the processed data can be fused with CT data for attenuation correction and combined interpretation.

A low-count processing protocol should be considered when SPECT/CT is done in areas of low tracer activity. An algorithm is used to amplify the data, which are then processed and fused with the CT data.

For more information, see the SNM Procedure Guideline for General Imaging and the SNM Procedure Guideline for SPECT/CT.

## E. Interpretation

When possible, images should be evaluated in conjunction with relevant anatomic images (e.g., CT, MRI, ultrasound). Where available, fusion imaging (SPECT/CT) should be considered for better characterization of tracer accumulation and more accurate lesion localization. The interpreting physician should carefully consider the clinical question raised in the request for <sup>111</sup>In-pentetreotide imaging.

Images are best viewed using a computer display with individualized physician-directed optimization of intensity and contrast. Three-dimensional rendering of the SPECT data and its review in cinematic display are encouraged.

Knowledge of normal tissue accumulation of <sup>111</sup>In-pentetreotide is important for study interpretation. This radiotracer can be seen in the pituitary, thyroid, liver, spleen, kidneys, bladder, and occasionally gallbladder. Intestinal activity is usually not present at 4 h but may be present at 24 h; thus, 48-h images may be necessary to clarify abdominal activity.

Additional issues to be taken into consideration include a comparison between pattern and intensity of uptake on early versus delayed images, the sensitivity of <sup>111</sup>In-pentetreotide

for the detection of the tumor type of interest as it relates to histology and expression/density of somatostatin receptor subtypes, and potential sources of false-negative and false-positive results (see section IX).

## F. Clinical Utility in Specific Tumor Types

### 1. Gastroenteropancreatic neuroendocrine tumors

In peptide hormone-producing gastroenteropancreatic endocrine tumors, including gastrinomas, insulinomas, vasoactive intestinal polypeptide-secreting tumors, glucagonomas, as well as nonfunctioning tumors, the sensitivity is generally high and varies depending on the tumor expression of somatostatin receptors. The sensitivity for insulinoma may be only 25%–60% because of the lower incidence of somatostatin receptors, especially subtype 2 (7,9,30,31)

### 2. Pheochromocytomas, neuroblastomas, and paragangliomas

In pheochromocytomas, neuroblastomas, and paragangliomas, sensitivity is greater than 85%. Imaging with <sup>111</sup>In-pentetreotide may be particularly useful in detecting primary lesions and metastases in unexpected (extraadrenal) sites not investigated by CT or MRI, when multiple tumors are suspected, or if conventional anatomic imaging is negative or equivocal. Tumors in the adrenal glands may be difficult to detect because of high renal activity; imaging with <sup>123</sup>I- or <sup>131</sup>I-metaiodobenzylguanidine may therefore be preferable for tumor localization in the adrenal area (32). <sup>111</sup>In-pentetreotide and <sup>123</sup>I/<sup>131</sup>I-metaiodobenzylguanidine have complementary roles in the evaluation of malignant pheochromocytomas, neuroblastomas, and paragangliomas (33).

### 3. Medullary thyroid carcinoma

In medullary thyroid carcinoma, sensitivity is 50%–75% (9,31). The use of SPECT/CT (for liver metastases) or comparison with <sup>123</sup>I-sodium iodide scintigraphy (for intrathyroidal tumors) may increase the rate of lesion detection, especially when the uptake of <sup>111</sup>In-pentetreotide in these organs is homogeneous. <sup>111</sup>In-pentetreotide may be considered for imaging of the oxyphil variant of follicular cell-derived thyroid cancers (34).

### 4. Carcinoid tumors

In carcinoid tumors, sensitivity is 86%–95%. For extrahepatic lesions larger than 1 cm in diameter, sensitivity may exceed 90%. Hepatic lesions may appear isointense relative to surrounding liver parenchyma; therefore, SPECT (with or without CT) imaging of the liver is recommended even if planar images appear normal. Sensitivity is lower for poorly differentiated (atypical) carcinoid tumors.

### 5. Intracranial tumors

In meningioma, sensitivity and specificity of 100% and 50%, respectively, have been reported by some (35). Medulloblastoma sensitivity is 61%–93%. <sup>111</sup>In-pentetreotide scintigraphy may be used for postoperative follow-up of meningioma. Grade I and II astrocytomas are also somatostatin receptor-positive, grade III astrocytomas may or may

**TABLE 1**  
Radiation Dosimetry: Adults\*

Radiopharmaceutical	Administered activity		Spleen (organ receiving largest dose)		Effective dose	
	MBq	mCi	mGy/MBq	rad/mCi	mSv/MBq	rem/mCi
<sup>111</sup> In-pentetreotide	222	6	0.57	2.1	0.054	0.20

\*Adapted from ICRP 106 (37).

not be, and grade IV astrocytomas (glioblastoma multiforme) are typically somatostatin receptor–negative. Localization of <sup>111</sup>In-pentetreotide in an astrocytoma also requires that the blood–brain barrier be impaired.

### VII. DOCUMENTATION/REPORTING

In addition to the general information to be provided in each nuclear medicine report as recommended in the SNM Guideline on General Imaging, it is suggested that the report contain the following information:

#### A. Indication

The report should include clinical findings, results of laboratory tests (e.g., neuroendocrine 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).

#### B. Relevant Medications

The report should describe relevant medications, including octreotide therapy and the length of time since it was discontinued, chemotherapy, and laxatives, if given.

#### C. Procedure Description

The procedure should be described, including the timing of imaging relative to radiopharmaceutical administration; areas imaged; whether SPECT or SPECT/CT was performed, and its timing and body areas included.

#### D. Study Limitations

The referring physician may be reminded that some tumors can lack somatostatin receptors or the appropriate receptor subtypes and, therefore, might not be detected. The differential diagnosis should consider the many potential causes for a false-positive study, as listed in section IX.D.

### VIII. EQUIPMENT SPECIFICATION

A  $\gamma$ -camera (preferably dual-head) with medium-energy collimation should be used. The use of a hybrid SPECT/CT camera is strongly encouraged for selected body areas, when available and indicated.

### IX. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION CONCERNS

Before the administration of <sup>111</sup>In-pentetreotide, the radiochemical purity of the preparation should be tested according to the manufacturer’s instructions. The product should not be used if radiochemical purity is less than 90%.

The radiopharmaceutical should be stored at or below 25°C (77°F) between preparation and administration and should be used within 6 h of preparation (15).

<sup>111</sup>In-pentetreotide should be inspected visually before administration. Preparations containing particulate matter or color should not be administered.

#### A. Potential Causes for a False-Positive Interpretation

Accumulation of <sup>111</sup>In-pentetreotide in the nasopharynx and pulmonary hilar areas may be seen with respiratory infections.

Diffuse pulmonary or pleural accumulation of <sup>111</sup>In-pentetreotide can be observed following radiation therapy to the lung or bleomycin therapy.

The tracer may accumulate at recent surgical and colostomy sites.

Accumulation of the tracer in normal structures (pituitary, thyroid, liver, spleen, kidneys, bowel, gallbladder, ureters, bladder, stimulated adrenal glands) and in multiple nonneoplastic disorders (some listed in Section III.C) must

**TABLE 2**  
Radiation Dosimetry: 15-Year-Old Children\*

Radiopharmaceutical	Weight-adjusted administered activity		Spleen (organ receiving largest dose)		Effective dose	
	MBq/kg	mCi/kg	mGy/MBq	rad/mCi	mSv/MBq	rem/mCi
<sup>111</sup> In-pentetreotide	3	0.08	0.79	2.9	0.071	0.26

\*Adapted from ICRP 106 (37).

**TABLE 3**  
Radiation Dosimetry: 5-Year-Old Children\*

Radiopharmaceutical	Weight-adjusted administered activity		Spleen (organ receiving largest dose)		Effective dose	
	MBq/kg	mCi/kg	mGy/MBq	rad/mCi	mSv/MBq	rem/mCi
<sup>111</sup> In-pentetreotide	3	0.08	1.8	6.7	0.16	0.59

\*Adapted from ICRP 106 (37).

be kept in mind. Caution must be used to avoid interpreting physiologic gallbladder activity as hepatic metastasis.

In breast-feeding women, physiologic uptake may be seen in the breast.

**B. Potential Causes for a False-Negative Interpretation**

The presence of unlabeled somatostatin, either as a result of octreotide therapy (patients will often have decreased tracer localization to the spleen) or production of somatostatin by the tumor itself, may lower tumor detectability.

The absence of somatostatin receptor subtype 2, variable tumor differentiation, and variable receptor expression also influence tumor detectability. This is a consideration especially with insulinomas and medullary thyroid carcinomas.

Low target-to-background ratio may cause a false-negative interpretation. Small liver metastases of neuroendocrine tumors may appear isointense relative to surrounding normal liver. Correlation with anatomic imaging, SPECT/CT, or subtraction scintigraphy with sulfur colloid may be considered in such cases.

**X. RADIATION SAFETY IN IMAGING**

See also Section X of the SNM Guideline for General Imaging.

It is the position of SNM that patient exposure to ionizing radiation should be at the minimum level consistent with obtaining a diagnostic examination. Reduction in patient radiation exposure may be accomplished by administering less radiopharmaceutical when the technique or equipment used for imaging can support such an action. Each patient procedure is unique, and the methodology to achieve minimum exposure while maintaining diagnostic accuracy needs to be viewed in this light. Radiopharmaceutical dose ranges outlined in this document should be considered as a guide. Dose reduction techniques should be used when appropriate. The same principles should be applied when CT is used in a hybrid imaging procedure. CT acquisition protocols should be optimized to provide the information

[Table 1] needed while minimizing patient radiation exposure. In particular, dose reduction in pediatric imaging is always

[Table 2] desirable, as long as image quality is maintained (36).

[Table 3] Tables 1–3 summarize the radiation dosimetry for adults,

15-y-old children, and 5-y-old children. For the pregnant or potentially pregnant patient, Table 4 provides dose estimates to the fetus (no information about possible placental crossover of this compound was available). For the breast-feeding patient, International Commission on Radiological Protection (ICRP) Publication 106, Appendix D (37), suggests that no interruption of breastfeeding is needed for <sup>111</sup>In-pentetreotide. [Table 4]

**XI. ISSUES REQUIRING FURTHER CLARIFICATION**

Since <sup>111</sup>In-pentetreotide elimination in patients with impaired renal function has not been studied, possible adjustment of administered activity in these patients needs to be clarified.

The role of <sup>111</sup>In-pentetreotide scintigraphy in breast carcinoma, renal cell carcinoma, Hodgkin and non-Hodgkin lymphoma, and other tumors (see section III), 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.

Recent studies have suggested that imaging with <sup>111</sup>In-pentetreotide and <sup>18</sup>F-FDG PET may be complementary and that abnormalities on either imaging modality predict a worse outcome in patients with neuroendocrine tumors. Further work is needed (38,39).

Neuroendocrine tumor imaging with conjugates of octreotide labeled with positron emitters (e.g., <sup>68</sup>Ga-DOTATOC) may have higher sensitivity and accuracy when compared with <sup>111</sup>In-pentetreotide; this issue requires further study (40).

The potential improvement in sensitivity and specificity of imaging such a heterogeneous group of tumors with a

**TABLE 4**  
Dose Estimates to the Fetus (41)

Stage of gestation	mGy/MBq	rad/mCi	mGy	rad
Early	0.082	0.30	18	1.8
3 mo	0.060	0.22	13	0.13
6 mo	0.035	0.13	7.8	0.78
9 mo	0.031	0.11	6.9	0.69

variable expression of different somatostatin receptor subtypes will depend on the future development and availability of a larger variety of radiopharmaceuticals (labeled either with single-photon emitters or positron emitters).

## XII. ACKNOWLEDGMENTS

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#### XIV. APPROVAL

This practice guideline was approved by the Board of Directors of the SNM on July 19, 2011.