

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Somatostatin Receptor Imaging with ^{111}In -Pentetreotide

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Introduction

The purpose of this guideline is to assist nuclear medicine practitioners in performing, interpreting, and reporting the results of somatostatin receptor scintigraphy with ^{111}In -pentetreotide. It is not this guideline's aim to give recommendations on the use of PET tracers for somatostatin receptor imaging (SRI). The reason for this is that valid comparisons between state of the art SRI with ^{111}In -pentetreotide and these newer PET imaging methods are lacking, and that these newer methods have not been fully validated. Besides, because of the local production of PET radiopharmaceuticals and the diversity of peptide analogs that are applied, each with a different affinity profile and therefore potentially a different biodistribution and a different tumor detection sensitivity, it is virtually impossible to make guidelines for the application of these PET radiopharmaceuticals. The general recommendations on patient preparation and image interpretation, however, do apply. This guideline is adapted from the procedure guideline for somatostatin receptor

scintigraphy with ^{111}In -pentetreotide, published by the Society of Nuclear Medicine [1]. $^{99\text{m}}\text{Tc}$ -Depreotide (Neotect[®]) is another commercially available somatostatin analog that has been approved specifically for the detection of lung cancer in patients with pulmonary nodules [2]. Because of the relatively high abdominal background and the impossibility of performing delayed imaging due to the short half-life of the tracer, it is less suited for the detection of abdominal neuroendocrine tumors [3].

Somatostatin is a regulatory peptide widely distributed in the human body, in particular in the central and peripheral nervous system, in the endocrine glands, in the immune system as well as in the gastrointestinal tract. In all these tissues, somatostatin action is mediated through membrane-bound receptors, of which five have been cloned (sst1–sst5) [4]. They all belong to the family of G-protein-coupled receptors. Only sst2, sst5 and, to some extent, sst3 have a high affinity for the commercially available synthetic octapeptide octreotide [5]. Somatostatin receptors are expressed in several normal human tissues, including brain, pituitary, gastrointestinal

Table 1. Sensitivity of SRI using pentetreotide

<i>High sensitivity</i>
Pituitary tumors [14]
GEPNETs
Gastrinomas [15, 16]
Nonfunctioning endocrine pancreatic tumors [17, 18]
Functioning endocrine pancreatic tumors except insulinomas [17, 18]
Carcinoids [19–22]
Parangliomas [23–25]
Small cell lung cancer [26–29]
Meningiomas [30, 31]
Sarcoidosis and other granulomatous diseases [12, 32]
Graves' disease and Graves' ophthalmopathy [33, 34]

<i>Intermediate sensitivity</i>
Insulinomas [17, 35]
Medullary thyroid carcinoma [36–38]
Differentiated thyroid carcinoma (including Hurthle cell carcinoma) [39–41]
Breast cancer [42]
Lymphoma (NHL, HL) [43, 44]
Pheochromocytoma [45]
Astrocytoma [31]

High sensitivity = Detection rate >75%; intermediate sensitivity = detection rate 40–75%. Sensitivity is either patient- or lesion-based. GEPNET = Gastroenteropancreatic neuroendocrine tumor; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma.

tract, pancreas, thyroid, spleen, kidney, immune cells, vessels and peripheral nervous system [6–9].

Somatostatin receptors have been identified *in vitro* in a large number of human neoplasias. A high incidence and density of somatostatin receptors are found in particular in neuroendocrine tumors, such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer and small cell lung carcinoma [10]. Tumors of the nervous system including meningioma, neuroblastoma and medulloblastoma also very often express a high density of somatostatin receptors. But also tumors not known to classically originate from endocrine or neural cells, such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, sarcoma and gastric cancer can express somatostatin receptors. In the majority of these tumors, the sst2 receptor subtype is predominantly expressed, although low amounts of other somatostatin receptor subtypes may be concomitantly present [11]. It should also be emphasized that selected non-tumoral lesions may express somatostatin receptors. For instance,

active granulomas in sarcoidosis express somatostatin receptors on epithelioid cells [12] and inflamed joints in active rheumatoid arthritis express somatostatin receptors, preferentially located in the proliferating synovial vessels [13]. The expression of somatostatin receptor is therefore not specific for tumoral pathologies.

Imaging Results in Neuroendocrine and Other Tumors

Imaging results in tumors and other diseases are listed and subdivided according to reported sensitivity of SRI in table 1.

Normal Scintigraphic Findings and Artifacts

Normal scintigraphic features include visualization of the thyroid, spleen, liver, and kidneys, and the pituitary in some of the patients. Also, the urinary bladder and bowel are usually visualized to variable degrees. The visualization of the pituitary, thyroid, and spleen is due to receptor binding. Uptake in the kidneys is for the most part due to re-absorption of the radiolabeled peptide in the renal tubular cells after glomerular filtration. There is predominant renal clearance of the somatostatin analog, although hepatobiliary clearance into the bowel also occurs, necessitating the use of laxatives in order to facilitate the interpretation of abdominal images.

False-positive results of SRI have been reported. In virtually all cases the term 'false-positive' is a misnomer because somatostatin receptor-positive lesions that are not related to the pathology for which the investigation is performed, are present. Many of these have been reviewed by Gibril et al. [46]. The most common of these are listed in table 2 (which is not exhaustive).

Diminished uptake in the spleen due to ongoing treatment with (unlabeled) octreotide may occur, which may be accompanied by a lower liver uptake. In case of hepatic metastases, this phenomenon may be misinterpreted as a better uptake in liver metastases. During octreotide treatment, the uptake of [¹¹¹In-DTPA⁰]-octreotide in somatostatin receptor-positive tumors is also diminished. This may lead to a lower detection rate of somatostatin receptor-positive lesions, although there are also literature reports of improved tumor-to-background ratio after pretreatment with nonradioactive octreotide. A number of causes for a potential false-negative study interpretation are given in table 3.

Common Indications

- Detection and localization of a variety of neuroendocrine and other tumors and their metastases
- Staging patients with neuroendocrine tumors
- Follow-up of patients with known disease to evaluate potential recurrence
- Selection of patients with metastatic tumors for peptide receptor radionuclide therapy and prediction of the effect of peptide receptor radionuclide therapy

Procedure

Patient Preparation

- When appropriate and clinically feasible, therapy with short-acting somatostatin analogs should be discontinued for 24 h before ¹¹¹In-pentetreotide administration. Such therapy can be resumed the day after injection of the radiopharmaceutical. Long-acting preparations should preferably be stopped 5–6 weeks before the study, and patients should be switched to short-acting formulations up to 1 day before the study. In follow-up studies, it may be more convenient to plan the injection of the radiopharmaceutical just before a new administration of the long-acting formulation is due. The reader should be aware that in such a condition, tumor and spleen uptake may be diminished due to receptor occupancy
- To reduce radiation exposure, patients should be well hydrated before and for at least 1 day after injection
- Laxatives are advised, especially when the abdomen is the area of interest. A mild oral laxative may be administered in the evening before injection and in the evening after injection. The need for bowel preparation should be assessed on an individual basis and laxatives should not be used in patients with active diarrhea
- There is no need for fasting prior to the investigation
- The feasibility of the investigation in patients on hemodialysis (with imaging after dialysis) should be discussed with local nephrologists and radiation protection experts

Precautions

- In patients suspected of having insulinoma, an intravenous infusion of glucose should be available because of the potential for inducing severe hypoglycemia

Table 2. Pitfalls and causes of potential misinterpretation of positive results

Radiation pneumonitis
Accessory spleen
Focal collection of stools
Surgical scar tissue
Gallbladder uptake
Nodular goiter
Ventral hernia
Bacterial pneumonia
Respiratory infections
Common cold (nasal uptake)
Cerebrovascular accident
Concomitant granulomatous disease
Diffuse breast uptake
Adrenal uptake
Urine contamination
Concomitant second primary tumor

Table 3. Causes of potential misinterpretation of negative results

Presence of unlabeled somatostatin, either because of octreotide therapy or resulting from production of somatostatin by the tumor itself, may lower tumor detectability
Different somatostatin receptor subtypes have different affinities for the radioligand; variable tumor differentiation and receptor expression also influence tumor detectability. This may be important especially in patients with insulinomas and medullary thyroid carcinomas
Liver metastases of neuroendocrine tumors may appear iso-intense because of a similar degree of tracer accumulation by the normal liver. Correlation with anatomic imaging and/or SPECT imaging may be helpful

- ¹¹¹In-pentetreotide should not be injected into intravenous lines for or together with solutions for total parenteral nutrition
- The usual precautions and considerations for nuclear medicine investigations in pregnant or breastfeeding women apply

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 or MRI), laboratory results (tumor markers), history of recent surgery, chemotherapy, radiation therapy, and octreotide therapy should be obtained

Radiopharmaceutical

- ¹¹¹In-pentetreotide is a [¹¹¹In-DTPA⁰] conjugate of octreotide, a somatostatin analog (OctreoScan). The recommended administered activity is 185–222 MBq (5–6 mCi) in adults and 5 MBq/kg (0.14 mCi/kg) in children. The amount of pentetreotide injected is 10–20 µg; this dose is not expected to have a clinically significant pharmacologic effect. ¹¹¹In-pentetreotide is cleared rapidly from the blood. Excretion is almost entirely through the kidneys (50% of the injected dose is recovered in the urine by 6 h, 85% within 24 h). Hepatobiliary excretion is only about 2% of the administered dose
- The effective dose equivalent is 0.054 mSv/MBq. For a full patient dose of 222 MBq this is 12 mSv
- Before the administration of ¹¹¹In-pentetreotide, the labeling yield of the radiopharmaceutical should be tested according to the manufacturer's instructions
- The radiopharmaceutical should be used within 6 h of preparation
- ¹¹¹In-pentetreotide should be inspected visually before administration. Preparations containing particulate matter or color should not be administered

Image Acquisition

- Patients should void before imaging
- Images are acquired at 4 and 24 h or 24 and 48 h after injection. The 48-hour images may be needed when there is significant bowel activity at 24 h, which may potentially obscure lesions. Four-hour images may be obtained to enable evaluation before appearance of activity in the gut, but since the tumor-to-background ratio is lower at 4 h than at 24 and 48 h, some lesions may be missed at 4 h
- 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 photopeaks of ¹¹¹In (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/image. For whole-body images using a dual-head camera, acquisition should be for a minimum of 30 min (head to upper femurs) and longer for the entire body (e.g., a speed of up to 3 cm/min has been suggested) 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 on the clinical history, should be per-

formed preferably with a multi-detector gamma camera. Early and delayed SPECT (i.e. 4 and 24 h after injection) may be helpful in distinguishing bowel activity from pathological lesions. If only one SPECT acquisition is obtained, acquisition at 24 h is preferred because of a higher target-to-background ratio. Although imaging systems may vary, an example of potentially useful acquisition parameters for a multi-detector system are the following: 3° angular sampling, 128 × 128 matrix, 360° rotation, 20–30 s/stop

Interpretation Criteria

- When possible, images should be evaluated in conjunction or fused with relevant anatomic images (e.g., CT or MRI)
- The optimal time interval to localize tumors is 24 h after injection or later. At 4 h the background activity may be high. Nevertheless, early images may be important for comparison and evaluation of abdominal activity imaged at 24 h
- Knowledge of normal tissue accumulation of ¹¹¹In-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 h, but may be present at 24 h; images at 48 h may be necessary to clarify abdominal activity

Reporting

- In addition to the general information to be provided in each nuclear medicine report, it is suggested that the report contain the following information
- *Indication:* 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, and chemotherapy)
- *Relevant medications:* For example, octreotide therapy and, when stopped, chemotherapy and/or laxatives, if given
- *Procedure description:* Timing of imaging relative to radiopharmaceutical administration; areas imaged; whether SPECT was performed and, if so, its timing and body areas included
- *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 table 2

List of Participants

List of Participants of the Consensus Conference on the ENETS Guidelines for the Standard of Care for the Diagnosis and Treatment of Neuroendocrine Tumors, Held in Palma de Mallorca (Spain), November 28 to December 1, 2007

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