Somatostatin-receptor Scintigraphy

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1. Introduction

Somatostatin is a peptide hormone. It acts primarily on the central nervous system, endocrine glands, the immune system and gastrointestinal tract. Action is mediated via membrane receptors. Five different somatostatin receptors are known (SST1-SST5). Somatostatin receptors are present in the brain, pituitary gland, thyroid gland, pancreas, spleen, immune cells, blood vessels and autonomous nervous system. Overexpression of somatostatin receptors has been found in many tumours, mainly neuroendocrine tumours and benign disease processes including sarcoidosis, other granulomatous disease, Graves' disease and Graves' ophthalmopathy, etc. In the majority of these tumours and benign diseases SST2 is expressed prominently, with lower expression of other subtypes. Indium-111-pentetreotide ([^{111}In-DTPA]-octreotide) is an octapeptide analogue of somatostatin, which is stable in vivo. It binds with high affinity to SST2 and with lower affinity to SST3 and SST5. After intravenous injection, ^{111}In-pentetreotide is rapidly cleared from the blood pool. It does not cross the blood-brain barrier. Excretion is predominantly via the kidneys (about 85% within 24 h) and to a lesser extent via liver and biliary system into the gut (about 2%).
Lesions with receptor overexpression can be visualized by planar scintigraphy and SPECT.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

a. Detection and localisation of somatostatin-receptor positive tumours and their metastases; often neuroendocrine tumours. Specific tumours and benign diseases which can be detected with high sensitivity (detection rate >75%) are: pituitary tumours, gastroenteropancreatic neuroendocrine tumours (GEPNETs), paragangliomas, small-cell lung cancer, meningioma, Merkel cell-tumour. Within the group of GEPNETs, gastrinoma, non-functioning endocrine pancreatic tumours, functioning endocrine pancreatic tumours (except insulinomas) and carcinoids can be detected with high sensitivity. Somatostatin-receptor scintigraphy with ^{111}In-pentetreotide has intermediate sensitivity (detection rate 40-75%) for detection of insulinomas, medullary thyroid carcinomas, differentiated thyroid carcinomas, breast cancers, lymphomas, pheochromocytomas and astrocytomas.
b. Detection of recurrence or progression of disease during follow-up of patients with known SST-positive disease.
c. Monitoring of the effects of surgery, radiation therapy, chemotherapy, embolization, etc.
d. Prediction of response to therapy with somatostatin analogues and evaluation of somatostatin-receptor status during follow-up.

e. Selection of patients eligible for peptide receptor radionuclide therapy.
f. Visualization of non-neoplastic diseases involving accumulation of lymphocytes and macrophages: granulomas (e.g. tuberculosis and sarcoidosis), Hodgkin's disease, non-Hodgkin lymphoma and autoimmune diseases (e.g. Graves' disease and rheumatoid arthritis).

4. Relation to other diagnostic procedures

Due to its high sensitivity, somatostatin-receptor scintigraphy has a key role in the diagnosis and staging of neuroendocrine tumours. Other imaging methods, like CT, MRI and/or ultrasound are very useful to confirm the presence of true lesions, to precisely localise lesions and to help discriminate true lesions from physiological or otherwise unrelated accumulation of ^{111}In-pentetreotide. Hybrid SPECT/CT makes specific reading more convenient and more accurate than SPECT alone due to the precise anatomical reference within the patient.

Newer radioactive somatostatin analogues (e.g. ^{68}Ga-DOTA-octreotate) have been developed for PET imaging. The advantages of ^{68}Ga based somatostatin receptor PET are many (better contrast and resolution, shorter imaging time, lower radiation burden), but it is currently not registered for routine clinical use and it is not widely available yet.

In general, adrenal pheochromocytomas are better visualized by ^{123}I-MIBG than by ^{111}In-pentetreotide scintigraphy. For metastatic pheochromocytoma discrepancies may occur, even within a single patient: some lesions are better visible with ^{123}I-MIBG, others with ^{111}In-pentetreotide. Most neuroblastomas are equally well visualized compared to ^{123}I-MIBG scintigraphy. The sensitivity of ^{111}In-pentetreotide scintigraphy for detection of neuroendocrine tumours and paragangliomas is clearly better than MIBG scintigraphy.

^{18}F-FDG PET and PET/CT commonly have low sensitivity for the detection of well-differentiated neuroendocrine tumours. However, poorly differentiated or de-differentiated and rapidly progressive neuroendocrine lesions may demonstrate intense ^{18}F-FDG uptake. Especially in patients with advanced neuroendocrine tumours and low or absent visualisation by ^{111}In-pentetreotide scintigraphy, additional ^{18}F-FDG-PET/CT should be considered as part of the work-up. The exact role of ^{18}F-FDG PET/CT in the management of patients with neuroendocrine tumours has not yet been established.

5. Medical information necessary for planning

a. Relevant symptoms and signs indicating (possible) SST-positive disease.
b. Relevant blood results (e.g. tumour markers), imaging results and cytology or histology results indicating (possible) SST-positive disease.
c. Possible localisation of lesions, based on physical examination or imaging.
d. Relevant medication, in particular dosage and last administration of short-acting or long-acting somatostatin analogues.

6. Radiopharmaceutical

Tracer:	^{111}In-pentetreotide
Radionuclide:	Indium-111
Activity:	200 MBq (10 µg peptide)
Administration:	intravenous

7. Radiation safety

a. Radiation exposure

The effective dose equivalent is 0,054 mSv/MBq in adults, 0,071 mSv/MBq in 15 year old children and 0,16 mSv/MBq in 5 year old children. The organ which receives the largest dose is the spleen, with 0,57 mSv/MBq in adults, 0,79 mSv/MBq in 15 year old children and 1,8 mSv/MBq in 5 year old children.

b. Pregnancy and lactation

The estimated dose to the foetus ranges from 0,082 mSv/MBq early in pregnancy to 0,031 mSv/MBq at 9 months, assuming no placental cross-over. No interruption of breastfeeding is needed for ^{111}In-pentetreotide.

8. Patient preparation/essentials for procedure

a. Therapy with short-acting somatostatin analogues should be discontinued preferably 24 h, but at least 12 h before the injection of ^{111}In-pentetreotide, except when continuation of therapy is clinically mandatory. Therapy with somatostatin analogues can be resumed the day after administration of the radiopharmaceutical. Long-acting somatostatin analogues should be interrupted for 5-6 weeks before the injection of ^{111}In-pentetreotide; patients can temporarily switch to short-acting analogues until 24 h before the study. A convenient alternative may be planning the injection of ^{111}In-pentetreotide just before the next administration of the long-acting somatostatin analogue is due. However, pharmacologically relevant levels of the somatostatin analogue may still be present, potentially interfering with the interpretation of ^{111}In-pentetreotide scintigraphy. Lower than expected activity in the spleen is then usually seen.
b. To reduce background activity and radiation exposure, patients should be well hydrated before and for at least 1 day after the injection.
c. There is no need for fasting before the study.
d. When pathology in the abdomen is to be evaluated, laxatives are advised to minimise bowel lumen activity, which may interfere with the interpretation of study. Laxatives should not be used in patients who already have active diarrhoea! A mild laxative (e.g. bisacodyl or lactulose) may be administered on the evening before injection and on the evening after the injection. The need for bowel preparation should be assessed on an individual basis.
e. In patients with a symptomatic insulinoma, an intravenous line is recommended and, if hypoglycaemia is present, i.v. glucose should be administered.
f. The feasibility of ^{111}In-pentetreotide scintigraphy in patients on haemodialysis (with imaging after dialysis) should be discussed with the local nephrologist and radiation protection expert.

9. Acquisition and processing

a. Patients should void immediately before the start of the acquisition.
b. Planar spot views and/or whole body scintigraphy are routinely obtained 24 h after injection. Additional images of the abdomen at 48 h or later can be useful to distinguish pathological lesions from bowel activity.
c. Planar spot images are generally obtained in supine position from anterior and posterior. Whole body acquisitions can also be used, but the speed of the system

should be low enough to ensure adequate count density for diagnostic quality of the study. Generally, a region from head to pelvis is adequate. For optimal detection sensitivity of small neck lesions, lateral spot views of the head/neck (with the head turned laterally and the camera close to the region) are recommended.

d. SPECT is essential in evaluating the upper abdomen and is often useful for other regions. SPECT can be acquired 24 h after injection, but additional SPECT at 48 h is also possible. The use of hybrid SPECT/CT is highly recommended, if available.
e. Acquisition is performed with a large-field-of-view gamma camera fitted with a medium-energy collimator. Symmetrical 20% energy windows are centred over both photo peaks of ^{111}In (173 keV and 247 keV). For SPECT, additional scatter energy windows may be obtained, depending on specific vendor recommendations and local preference.
f. Planar spot images are acquired for 15 min per image, using a 256x256 matrix. Whole-body images with a dual-head camera are obtained in a single pass, at a maximal speed of 3 cm/min, using a 256x1024 pixel matrix.
g. SPECT should be performed with a multi-detector system when possible. Acquisition of 90-120 views over 360° rotation, 30-45 sec/view using a 128x128 matrix is recommended. In hybrid SPECT/CT systems, low-dose CT is potentially useful for attenuation correction and anatomical localisation. In individual cases the potential benefits should be weighed against the additional radiation exposure from CT. The optimal CT acquisition and processing protocol is different for specific hybrid systems. For SPECT, iterative reconstruction with ordered-subsets expectation maximization is the recommended reconstruction algorithm. Specific parameters depend on vendor recommendations and local preferences. Particular attention should be given to reconstruction artefacts that may occur in low-count studies. Post-reconstruction filters should be chosen judiciously, as too little filtering may result in artefacts mimicking lesions and too much filtering may obscure real lesions.

10. Interpretation

- Normal tracer accumulation can be seen in the pituitary gland (variable) , thyroid, spleen and kidneys. Liver activity is less intense compared to splenic activity. The adrenal glands may be visualised. In the majority of patients, abdominal activity is present in bowels, gall bladder and urinary bladder at 24 h post injection. At 48 h post injection, upon repeat laxatives, this activity should disappear, or show a different distribution. Abnormal localisation of activity is highly suspicious for pathology. The intensity may vary from faint to very intense. SPECT/CT is very useful for specific interpretation.
- Abnormal activity in the nasopharyngeal region can be the result of respiratory infections. This abnormal activity can also be seen in the region of the trachea and hila, probably due to uptake in lymphocytes or macrophages.
- Patients treated with long- or short-acting somatostatin analogues may have decreased splenic uptake. Apparent receptor-mediated intensity in lesions may also be low with pharmacologically relevant levels of cold somatostatin analogue.
- Faint symmetrical activity in breast tissue is a common physiological finding. Focal uptake is suggestive of breast carcinoma.
- Bowel activity at 24 h post injection is mostly found in colon, from coecum to rectum

and may lead to false-positive interpretation.
- False-positive results can be due to urine contamination on the skin or clothes, (recent) surgery, external radiation to the lungs, and bleomycin therapy (abnormal pulmonary uptake).
- The sensitivity for detection of lesions is usually better using spot-view imaging compared to whole body imaging.
- Liver metastases from neuroendocrine tumours are sometimes not seen because receptor expression by the tumour is iso-intense to normal liver parenchyma.
- Positive scintigraphy with ^{111}In-pentetreotide reflects the presence of increased density of somatostatin receptors rather than malignant disease. This requires evaluation of the possibility that other disease characterised by high local somatostatin receptor concentrations may be present.
- In cases where scintigraphy shows large differences in lesion activity (e.g. "hot" and "cold" tumours), attention and careful evaluation of these lesions are advised. Although the intensity at which pathological processes are visible may vary considerably, the occurrence of synchronous tumours is not uncommon.

11. Report

In addition to the general information to be provided in each nuclear medicine report we suggest that the report contain the following information:
- A concise patient history
- Indication
- Relevant medication (patient preparation, somatostatin analogue therapy, withdrawal period, chemotherapy, etc.)
- Procedure description
- Findings (site of the lesion(s), uptake intensity, etc.)
- Study limitations

12. Literature

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