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GUIDELINES

^{111}In-pentetreotide scintigraphy: procedure guidelines for tumour imaging

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Abstract This document provides general information about somatostatin receptor scintigraphy with ^{111}In-pentetreotide. This guideline should not be regarded as the only approach to visualise tumours expressing somatostatin receptors or as exclusive of other nuclear medicine procedures useful to obtain comparable results. The aim of this guideline is to assist nuclear medicine physicians in recommending, performing, reporting and interpreting the results of ^{111}In-pentetreotide scintigraphy.

Keywords ^{111}In-pentetreotide scintigraphy · Tumour imaging · Procedure guidelines · Neuroendocrine tumours · Indications

This guideline summarises the views of the Oncology Committee of the EANM and reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.
The guidelines have been reviewed by the EANM Dosimetry Committee, the EANM Physics Committee and the EANM Radiopharmacy Committee.
The guidelines have been brought to the attention of the National Societies of Nuclear Medicine.

Aim

The aim of this document is to provide general information about somatostatin receptor scintigraphy with ^{111}In-pente-

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treotide, a [^{111}In-DTPA^{0}] conjugate of octreotide that binds to somatostatin receptors. This guideline should not be regarded as the only approach to visualise tumours expressing somatostatin receptors or as exclusive of other nuclear medicine procedures useful to obtain comparable results. The aim of this guideline is to assist nuclear medicine physicians in recommending, performing, reporting and interpreting the results of ^{111}In-pentetreotide scintigraphy. The corresponding guideline of the Society of Nuclear Medicine [1] and of the European Neuroendocrine Tumour Society [2] have been taken into consideration, as well as the most relevant literature on this topic.

Background

Somatostatin is a small, cyclic neuropeptide that is present in neurones and endocrine cells; it has a high density in the brain, peripheral neurones, endocrine pancreas and gastrointestinal tract. Naturally occurring somatostatin has a very short plasma half-life (1–3 min) and therefore synthetic analogues have been developed, including octreotide acetate. In the ^{111}In-pentetreotide ([^{111}In-DTPA^{0}]-octreotide) molecule, the biologically active ring of octreotide remains intact and a DTPA molecule is covalently coupled to the D-phenylalanine group so that it can be labelled with ^{111}In. ^{111}In-labelled pentetreotide specifically binds to somatostatin receptors, with particular affinity to subtypes 2 and 5. Somatostatin receptors have been identified on many cells of neuroendocrine origin; additionally, several non-neural and non-endocrine cells sometimes display somatostatin receptors with various degrees of density. Consequently, tumours deriving from cell types expressing somatostatin receptors may be imaged by somatostatin receptor scintigraphy [3, 4].

Somatostatin receptor scintigraphy has proven superior to conventional imaging modalities for the assessment of neuroendocrine tumours (NET). The detection rate was reported to be between 80 and 100% in different studies. Somatostatin receptor scintigraphy provides information regarding the content of somatostatin receptors that might indicate efficacy for treatment with octreotide or other somatostatin analogues [5–7]. Furthermore, there is evidence of a correlation between somatostatin receptor expression and prognosis, since patients with NET showing a positive profile on the scan have a better response to treatment with somatostatin analogues [8]. Limitations of somatostatin receptor scintigraphy include the evaluation of organs with higher physiological uptake (e.g. liver) and the detection of small lesions due to suboptimal physical resolution of the isotopes used for SPECT imaging [9–12].

Disease processes that may express somatostatin receptors and may thus be positive on somatostatin receptor scintigraphy include the following

Tumours with high expression of receptors [14–19]:

- Sympathoadrenal system tumours (phaeochromocytoma, neuroblastoma, ganglioneuroma and paraganglioma)
- Gastroenteropancreatic tumours (GEP) (e.g. carcinoids, gastrinoma, insulinoma, glucagonoma, VIPoma, etc.), functioning and non-functioning
- Medullary thyroid carcinoma
- Pituitary adenoma
- Merkel cell carcinoma
- Small cell lung cancer

Tumours with low expression of receptors:

- Breast carcinoma
- Melanoma
- Lymphomas
- Prostate carcinoma
- Non-small cell lung cancer
- Sarcomas
- Renal cell carcinoma
- Differentiated thyroid carcinoma
- Astrocytoma
- Meningioma

Non-neoplastic diseases [20, 21]:

- Autoimmune diseases
- Granulomas
- Thyroid-associated ophthalmopathy
- Post-radiation inflammatory disease
- Bacterial infections

Clinical indications

The main indication for ^{111}In-pentetreotide scintigraphy is the imaging of NET, originating more frequently from the gastroenteropancreatic tract (gastrinoma, insulinoma, glucagonoma, VIPoma, etc.) followed by the lungs. Less frequent NET localisations include the skin, the adrenal glands, the thyroid (medullary carcinoma) and the genital tract. Other tumours that usually display a high density of somatostatin receptors include sympathoadrenal system tumours [22–27].

In the management of patients with NET ^{111}In-pentetreotide scintigraphy can be used to:

- Localise primary tumours and detect sites of metastatic disease (staging)
- Follow up patients with known disease to detect residual, recurrent or progressive disease (re-staging)

- Monitor the effects of therapy (surgery, radiotherapy, chemotherapy or somatostatin analogue therapy)
- Select patients for peptide receptor radionuclide therapy
- Obtain a prognostic parameter for the response of subsequent therapy

Since the density of somatostatin receptors on NET may vary, the sensitivity of ^{111}In-pentetreotide is likely to vary among tumour types.

The sensitivity of ^{111}In-pentetreotide scintigraphy may theoretically be reduced in patients receiving therapeutic doses of octreotide, but this issue still needs to be clarified.

Precautions

- Pregnancy (suspected or confirmed). In the case of a diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure.
- Breastfeeding. If radiopharmaceutical administration is considered necessary, breastfeeding should be interrupted and can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv.
- The effects of ionising radiation from ^{111}In-pentetreotide administration must be carefully evaluated in subjects under 18 years of age [28, 29].
- In patients with clinically significant renal impairment, administration of ^{111}In-pentetreotide is not recommended because the impairment of the principal route of excretion will lead to delivery of an increased radiation dose. Interpretable scintigrams may be obtained after haemodialysis. Images obtained before dialysis are of poor diagnostic value because of circulating activity within the body. After dialysis a higher than usual uptake in liver, spleen and intestinal tract and a higher than usual activity in the circulation have been observed. Radiation safety information and precautions related to radioactive effluents must be considered in patients undergoing haemodialysis.
- It has been recommended by some authors to temporarily withdraw somatostatin analogue therapy (when possible) to avoid possible somatostatin receptor blockade (see patient preparation). In some patients the withdrawal of therapy might not be tolerated. However, this issue is still under debate.
- In diabetic patients receiving high doses of insulin the administration of pentetreotide may cause paradoxical hypoglycaemia via a temporary inhibition of glucagon secretion.

Pre-examination procedure

1. Patient preparation

   - The technologist or physician should give the patient a thorough explanation of the test.
   - It has been recommended by some authors to discontinue “cold” octreotide therapy (when possible and not contraindicated) to avoid possible somatostatin receptor blockade; however, there are even literature reports of improved tumour to background ratios following pre-treatment with non-radioactive octreotide. The time interval between interruption of therapy and ^{111}In-pentetreotide scintigraphy depends on the type of drugs used: 1 day is suggested for short-lived molecules and 3–4 weeks for long-acting analogues. However, this issue is still not definitely clarified.
   - Although only 2% of the administered dose undergoes biliary excretion, it is necessary to minimise the potential for visualising artefacts in the intestine when abdominal lesions are suspected. It is advised to administer a laxative, especially when the abdomen is the area of interest. A mild oral laxative should be administered on the day before injection and continued throughout the day(s) of imaging. In patients with insulinomas bowel cleansing must not be undertaken without consulting the endocrinologist in charge of the patient.
   - Ample fluid intake is necessary to reduce the radiation exposure. Patients must be well hydrated before and after injection.

2. Pre-injection

All information useful for a better interpretation of somatostatin receptor scintigraphy should be considered by the nuclear medicine physician:

   - Relevant history of suspected or known primary tumour.
   - Absence or presence of functional symptoms.
   - Laboratory test results (circulating hormones, tumour markers).
   - Results of any other imaging studies (CT, MRI, US, X-rays).
   - History of recent biopsy, surgery, chemotherapy, radiation therapy.
   - History of recent somatostatin analogue therapy.
   - There is no need for fasting before injection.

3. ^{111}In-pentetreotide injection, administered activity

   - ^{111}In-pentetreotide is commercially available as OctreoScan. The radiopharmaceutical should be administered using an indwelling catheter or but-

terfly needle, thus avoiding paravasal deposition of activity.

- The activity of the radiopharmaceutical to be administered should be determined after taking account of the Directive 97/43/EURATOM. It is expected that diagnostic reference levels (DRL) for radiopharmaceuticals will not to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied. For this reason the following activity for ^{111}In-pentetreotide should be considered only as a general indication, based on literature data and current experience. It should be noted that in each country nuclear medicine physicians should respect the DRLs and the rules stated by the local law. Activities higher than the DRLs must be justified.
- The activity reported in the literature ranges from 120 to 220 MBq (3.2–5.9 mCi), mean activity 175 MBq (4.7 mCi). The recommended activity to obtain a good imaging quality is about 200 MBq (5.4 mCi). However, activities lower than 200 MBq can be administered without loss of imaging quality adjusting the acquisition parameters accordingly. The experience in paediatric patients is very limited; when the use of the radiopharmaceutical is considered necessary in a child the activity should be reduced according to the recommendations of the EANM Paediatric Task Group. The organ which receives the largest radiation dose is spleen followed by kidneys and bladder (ICRP Publication 106, Ann ICRP, Vol 38(1–2), pp 133–135, 2008) [30–33].
- The maximum amount of pentetreotide injected is 10 μg; this amount is not expected to have any clinically significant pharmacological effect. The in vitro biological activity of ^{111}In-pentetreotide is approximately 30% of the biological activity of natural somatostatin. Intravenous administration of 20 μg of pentetreotide resulted in some patients in a measurable but very limited decrease in serum gastrin and serum glucagon levels of less than 24 h duration.
- ^{111}In-pentetreotide should not be injected into intravenous lines together with solutions for parenteral nutrition.
- The radiopharmaceutical should be used within 6 h of preparation.

4. Post-injection

Patients should void before scanning. Abundant fluid intake is required for 2 or 3 days following administration. Elimination of the extra fluid intake will help to flush out unbound labelled pentetreotide and non-peptide-bound ^{111}In by glomerular filtration. This will reduce the background noise as well as the radiation dose to kidneys and bladder.

Physiological ^{111}In-pentetreotide distribution

^{111}In-pentetreotide is rapidly cleared from the blood: 35% of the injected activity remains in the blood pool at 10 min and only 1% at 20 h after injection. Excretion is almost entirely through the kidneys: approximately 50% of the intravenously administered activity is found in the urine by 6 h and 85% within 24 h. Hepatobiliary excretion and elimination via the faeces account only for 2% of the total administered activity.

Somatostatin receptors are expressed by many neuroendocrine and non-neuroendocrine cells of the body, so different organs may be imaged by somatostatin receptor scintigraphy including the liver (approximately 2% at 24 h), spleen (approximately 2.5% at 24 h), pituitary, thyroid and kidneys. Stimulated adrenal glands may be faintly visualised. Other organs are shown at different times as a result of the clearance of ^{111}In-pentetreotide: gall bladder, bowel, renal collecting system, ureters and bladder.

Radiopharmaceutical: [^{111}In]pentetreotide

Description

Pentetreotide for labelling with ^{111}In is commercially available as OctreoScan®. It is supplied, as two vials:

Vial A: ^{111}In as $InCl_3$, 122 MBq (3.3 mCi)/1.1 ml
Vial B: 10 μg of lyophilised pentetreotide and excipients

Preparation

The contents of vial A are added to vial B according to the manufacturer's instructions. After reconstitution and labelling the solution contains ^{111}In-pentetreotide in trisodium citrate, citric acid, inositol, gentisic acid, ferric chloride and hydrochloric acid; 0.02 N. After reconstitution and labelling the pH of the aqueous solution is 3.8–4.3. The validity is 6 h after reconstitution.

Quality control

The radioactive concentration should be determined by measuring the activity of the vial in a calibrated ionisation chamber. Radiochemical purity may be confirmed using a TLC method. (Solid-phase ITLC-SG, mobile-phase 0.1 N

sodium citrate adjusted with HCl to pH 5, Rf: ^{111}In-pentetreotide 0.0, unbound ^{111}In 1.0). Labelling efficiency should be >95%.

Special precautions

The preparation may be diluted with 2–3 ml of sterile physiological saline if required.

Gamma camera quality control

A strict quality control programme should be routinely performed according to the rules of each country. Refer to the EANM Routine Quality Control Recommendations for Nuclear Medicine Instrumentation [34].

Image acquisition

1. Instrumentation

Gamma camera fitted with a medium-energy, parallel-hole collimator. Energy window: ^{111}In photopeaks (172 and 245 keV) with 20% windows summed in the acquisition frames. A large field of view gamma camera is required for total body imaging.

2. Acquisition modality

- Planar and SPECT images should be acquired at 4 and 24 h or 24 and 48 h post-injection. Four-hour images benefit from a low bowel activity but the radiopharmaceutical concentration in the sites of diseases could become significant later, which is why it is important to acquire two sets of images, with at least one SPECT acquisition. Spot views may be repeated at 48, 72 and/or 96 h post-injection to allow clearance of interfering bowel radioactivity. Between 24 and 48 h imaging a laxative therapy can be administered to achieve an improvement of target to non-target ratio of activity if the non-specific activity in the bowel is still high.
- Although the number of publications investigating the added value of CT coregistration for somatostatin receptor planar imaging and somatostatin receptor SPECT is limited, it has been suggested that coregistered CT can be used for attenuation correction and may improve the localisation of somatostatin receptor expressing lesions.
- Planar images: both anterior and posterior of head, neck, chest, abdomen, pelvis and lower extremities; 15 min per view; matrix size should match desired spatial resolution taking into account collimator selection.
- Whole body: maximum scanning speed of 3 cm/min. A whole-body image may substitute for anterior and posterior spot images of head/neck/chest/abdomen, however with lower sensitivity to detect lesions.
- SPECT: degrees of rotation: 360; number of projections: 120 in total; time per projection: 45 s; acquisition matrix: 64×64 word.

Planar and SPECT studies are preferably performed 24 h after injection of the radiopharmaceutical. Scintigraphic studies after both 24 and 48 h can be carried out with the same protocol. Repetition of scintigraphy after 48 h is especially indicated when 24-h scintigraphy shows accumulation in the abdomen, which may also represent radioactive bowel content.

Optional images

Four-hour images have a relatively high background radioactivity, but have the advantage of negligible bowel activity. High background radioactivity may have the effect of missing lesions, expressing a rather low density of somatostatin receptors.

Image processing

Due to the high variability of hardware and types of software of the gamma cameras, it is not possible to draw a general recommendation about imaging processing. SPECT data should be reconstructed and filtered according to the preference of the individual centres and recommendations of the manufacturer. Attenuation correction based on CT or radioactive sources should be applied if available. Iterative algorithms need to be validated carefully.

Image interpretation

Images should be evaluated by a nuclear medicine physician.

To evaluate somatostatin receptor scintigraphy images, the following items should be taken into consideration:

- Clinical issue raised in the request for ^{111}In-pentetreotide imaging
- Clinical history of the patient
- Knowledge of normal tissue accumulation and timing (e.g. intestinal activity is absent at 4 h but present at 24 h) and comparison between early and late images
- Anatomical localisation of the uptake according to other non-nuclear medicine imaging data
- Intensity of the ^{111}In-pentetreotide uptake
- Semiquantitative assessment of lesions, with tumour to background ratio may be useful in selected cases

- Clinical correlation with any other data from previous relevant clinical, biochemical and morphological examinations
- Sensitivity of ^{111}In-pentetreotide scintigraphy in detecting different tumour types, which is related to tumour histology, expression and density of somatostatin receptors and site of the lesion(s)
- The sensitivity in detecting lesions with limited uptake is better in most cases with static rather than whole-body images
- Causes of false-negative results
- Causes of false-positive results

Reporting

The nuclear medicine physician should record all information regarding the patient, a concise patient history, type of examination, date, radiopharmaceutical (administered activity and route), relevant medications (patient preparation, octreotide therapy, withdrawal period, chemotherapy, etc.), laboratory results, all data obtained by other imaging studies and the clinical question.

The report to the referring physician should describe:

1. The procedure (^{111}In-pentetreotide activity administered, timing of imaging, area imaged, SPECT performed, etc.).
2. Findings (site of the lesion(s), uptake intensity, etc.).
3. Comparative data (the findings should be related to previous information or results of other clinical or instrumental examinations).
4. Interpretation: a clear diagnosis should be made if possible, accompanied—when appropriate—by a description of the study limitations (potential causes of false-negative or false-positive results). In case the conclusive impression should require additional diagnostic examinations or an adequate follow-up, this must be recommended.

Sources of error

- The pituitary and the thyroid are faintly visible. Intense accumulation of radioactivity is seen in the spleen and kidneys. Accumulation in the liver can be compared to the intensity of the spleen.
- Radioactivity is almost always found in the bowel on the 24-h image. Caution must be used to avoid interpreting physiological colon activity as intestinal lesions. Radioactivity in the bowel on the 24-h image is most often localised within the colon, from the caecum to the rectum. On the 48-h image the signal is differently distributed or even gone upon laxation.
- On the 24-h image the gall bladder is often visible. The gall bladder is always visible on SPECT images, even if it is not visible on the planar image due to overprojection of the kidney and liver. Caution must be used since normal gall bladder activity may sometimes be confused with liver metastases.
- Patients with respiratory infections often show accumulation in the nasopharynx, and to a lesser extent in tracheal and pulmonary hilar areas, most probably due to radiopharmaceutical accumulation in the lymphocytes.
- Diffuse pulmonary or pleural accumulation can be observed after radiation therapy to the thoracic area or following bleomycin therapy. Patients on somatostatin analogue therapy can be recognised by reduced uptake in the spleen.
- The tracer may accumulate in areas of recent surgery and at colostomy sites.
- Contamination with urine of clothes and/or skin may cause false-positive images.
- Octreotide therapy or the endogenous production of somatostatin (by the tumour) may reduce tumour detectability.
- Variable tumour differentiation and heterogeneous expression of somatostatin receptor subtypes may influence the affinity for ^{111}In-pentetreotide and thereby tumour detectability.
- Liver metastases from neuroendocrine tumours are sometimes not seen because receptor expression by the tumour is isointense to that of normal liver cells.
- Women sometimes show slight tracer uptake in the breast region; such physiological uptake is symmetrical.
- It should be remembered that positive scintigraphy with ^{111}In-pentetreotide reflects the presence of an increased density of somatostatin receptors rather than malignant disease. Uptake is not specific for tumours. Positive scintigraphic results require evaluation of the possibility that other disease characterised by high local somatostatin receptor concentrations may be present. The intensity at which pathological processes are visible may vary considerably.

Issues requiring further clarification

- Many non-neuroendocrine tumours express somatostatin receptors and can thus be visualised using somatostatin receptor imaging (e.g. breast cancer, lymphomas, meningiomas, astrocytomas, renal cell carcinoma, etc.). The role of ^{111}In-labelled pentetreotide scanning in patients with these tumours has not been clearly demonstrated and should be further investigated.
- Other radiolabelled somatostatin analogues or radiopharmaceuticals for tumours expressing somatostatin

receptors are available. Among these, also radiopharmaceuticals for PET can be used. Even if ^{18}F-FDG has been successfully and widely employed in oncology, it has not demonstrated a satisfactory uptake in well-differentiated neuroendocrine tissues. FDG uptake is poor in well-differentiated NET with low glucose metabolism. However, PET with other radiopharmaceuticals labelled with ^{68}Ga (DOTA-TOC, DOTA-NOC and DOTA-TATE) has demonstrated advantages over scintigraphic imaging.

- Little is known about the ^{111}In-pentetreotide elimination in patients with impaired renal function. Dose adjustment in these patients is a topic for further studies.

Disclaimer

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

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