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GUIDELINES

Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE

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Abstract The aim of these guidelines is to assist nuclear medicine physicians in recommending, performing, reporting and interpreting the results of somatostatin (SST) receptor PET/CT imaging using ^{68}Ga-DOTA-conjugated peptides, analogues of octreotide, that bind to SST receptors. This imaging modality should not be regarded as the only approach to visualizing tumours expressing SST receptors or as excluding other imaging modalities useful for obtaining comparable results. The corresponding guidelines of ^{111}In-pentetreotide scintigraphy imaging have been considered and partially integrated with this text. The same has been done with the relevant and recent literature in this field and the final result has been discussed by distinguished experts.

Keywords PET · Tumour imaging · Procedure guidelines · Peptides · Neuroendocrine tumours · Indications

These guidelines summarize the views of the Oncology Committee of the EANM and reflect 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.

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Background information and definitions

The rationale for the employment of ^{68}Ga-DOTA-conjugated peptides for the assessment of somatostatin (SST) receptor-expressing tumours is based on the high affinity of these compounds for SST receptors [1–6]. SST is a small, cyclic neuropeptide that is present in neurons and endocrine cells; it has a high density in the brain, peripheral neurons, endocrine pancreas and gastrointestinal tract. Naturally occurring SST has a very low metabolic stability, and therefore more stable, synthetic analogues have been developed [5, 6].

Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms that arise from endocrine cells within glands (adrenal medulla, pituitary, parathyroid) or from endocrine islets in the thyroid, the pancreas, or the respiratory and gastrointestinal tract. The majority of NETs express SST receptors, so they can be effectively targeted and visualized with radiolabelled SST analogues in vivo [6–15].

Scintigraphy with radiolabelled SST analogues, first with a ^{123}I label and subsequently with a ^{111}In and ^{99m}Tc label, has proven useful in diagnosing SST receptor-positive tumours [5–15]. The detection rate has been reported to be between 50% and 100% in different studies. This method also shows

the content of SST receptors, which might indicate the potential for treatment with octreotide or other SST analogues. Furthermore, there is evidence of a correlation between SST receptor expression and prognosis, since patients with a NET showing a positive profile on the scan have a better response to treatment with SST analogues [14, 15]. Although SST receptor scintigraphy shows high efficacy for whole-body imaging, there are some limitations in organs with higher physiological uptake, e.g. liver, and in terms of detection of smaller lesions due to suboptimal physical resolution of the used isotopes for SPECT imaging [16, 17].

More recently, PET with the ^{68}Ga-DOTA-conjugated peptides [^{68}Ga-DOTA^{0}-Tyr^{3}]octreotide (^{68}Ga-DOTA-TOC, ^{68}Ga-edotreotide), [^{68}Ga-DOTA^{0}-1NaI^{3}]octreotide (^{68}Ga-DOTA-NOC) and [^{68}Ga-DOTA^{0}-Tyr^{3}]octreotate (^{68}Ga-DOTA-TATE) has brought about dramatic improvements in spatial resolution and is increasingly being used in specialized centres [18–20]. Although ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE can all bind to SST receptor 2, they have different affinity profiles for other SST receptor subtypes [4]. In particular, ^{68}Ga-DOTA-NOC also shows a good affinity for SST receptors 3 and 5, ^{68}Ga-DOTA-TOC also binds to SST receptor 5 (although with lower affinity than DOTA-NOC). ^{68}Ga-DOTA-TATE has a predominant affinity for SST receptor 2.

Initial patient studies have demonstrated the potential of PET technology using ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE. In particular PET clearly offers higher resolution and improved pharmacokinetics as compared to SST receptor scintigraphy, with promising results for the detection of SST receptor-expressing tumours [16, 17], and provides prognostic information [21].

Tumours that may be visualized with ^{68}Ga-DOTA-conjugated peptide PET/CT

Tumours with high expression of receptors [22–29]:

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

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
- Ependymoma [30, 31]

Clinical indications

The primary indication of ^{68}Ga-DOTA-conjugated peptide PET/CT is for the imaging of NETs, which usually express a high density of SST receptors. It can also be used in the imaging of tumours other than NETs, particularly if treatment with radiolabelled therapeutic SST analogues is under consideration. ^{68}Ga-DOTA-conjugated peptide PET/CT cannot be considered as the first-choice functional imaging modality in the management of patients with tumours other than NETs, except for the determination of SST receptor status.

In the management of NETs ^{68}Ga-DOTA-conjugated peptide PET/CT is used to:

- Localize primary tumours and detect sites of metastatic disease (staging) [22–29, 32–34].
- Follow-up patients with known disease to detect residual, recurrent or progressive disease (restaging) [22–29, 32–34].
- Determine SST receptor status visually as well by using semiquantitative parameters like standardized uptake value (patients with SST receptor-positive tumours are more likely to respond to octreotide therapy) [35, 36].
- Select patients with metastatic disease for SST receptor radionuclide therapy (with ^{177}Lu or ^{90}Y-DOTA-peptides) [35, 36].

Monitoring response to therapy has been proposed [36] but still needs to be assessed as the change in receptor status does not necessarily indicate therapy response and dedifferentiation with loss of receptors must be taken into account.

The sensitivity of ^{68}Ga-DOTA-conjugated peptide PET/CT is likely to vary among tumour types, depending on the density of SST receptors. There are no data suggesting that ^{68}Ga-DOTA-conjugated peptides are useful for dosimetry. The sensitivity of ^{68}Ga-DOTA-conjugated peptide PET/CT may theoretically be reduced in patients receiving therapeutic doses of octreotide, but this issue still needs to be clarified.

Cautionary considerations

- Pregnancy (suspected or confirmed). In the case of a diagnostic procedure in a patient who is or may be pregnant, a clinical decision is necessary considering 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 radiation dose to the child would be lower than 1 mSv.
- The ionizing radiation from ^{68}Ga-DOTA-conjugated peptide administration must be carefully evaluated in subjects under 18 years of age. However, the radiation dose delivered to the whole body might be lower than administration of ^{111}In-pentetreotide.
- It has been recommended by some authors to temporarily withdraw SST analogue therapy (when possible) to avoid possible SST receptor blockade (see Patient preparation). In some patients the withdrawal of therapy might not be tolerated. However this issue is still under debate.

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 contra-indicated) to avoid possible SST receptor blockade; however there are literature reports of improved tumour-to-background ratios following pretreatment with nonradioactive octreotide. The time interval between interruption of therapy and ^{68}Ga-DOTA-conjugated peptide PET/CT 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 and many centres do not require octreotide withdrawal before PET scanning. The best option is to perform the PET/CT study just prior to the scheduled monthly dose of long-acting octreotide.
- No need for fasting before injection.

2. Before injection

All information useful for optimal interpretation of the study 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 (hormone or tumour marker levels)
- Results of other imaging modalities (CT, MRI, ultrasonography, plain radiography)
- History of recent biopsy, surgery, chemotherapy, radiotherapy or radionuclide therapy
- History of recent SST analogues (octreotide) therapy

3. Administered activity of ^{68}Ga-DOTA-conjugated peptides (DOTA-TOC, DOTA-NOC, DOTA-TATE)

- The radiopharmaceutical should be administered using an indwelling catheter to avoid extravasation.
- The activity of the radiopharmaceutical to be administered should be determined after taking account of Directive 97/43/EURATOM. Diagnostic reference levels (DRL) for radiopharmaceuticals should not be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied. It should be noted that in each country nuclear medicine physicians should respect the DRLs and the requirements of local laws. Activities higher than the DRLs must be justified. For these reasons the following activities for ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE should be considered only as general indications, based on literature data and current experience.
- The activity administered ranges from 100 to 200 MBq, also depending on the characteristics of the PET tomograph. The recommended activity to obtain a good quality image is at least 100 MBq. Experience in paediatric patients is very limited; when the use of a radiopharmaceutical is considered necessary in a child, the activity should be reduced according to the recommendations of the EANM Paediatric Task Group. The organ that receives the largest radiation dose is the spleen, followed by the kidneys and urinary bladder.
- Definitive dosimetric data for ^{68}Ga-DOTA-TOC , DOTA-NOC and DOTA-TATE are not yet available.
- The amount of ^{68}Ga-DOTA-conjugated peptide (DOTA-TOC, DOTA-NOC, DOTA-TATE) injected should be less than 50 μg (in discussion in PharmEur); this amount would be expected not to have any clinically significant pharmacological effect. The radiopharmaceutical should not be injected into intravenous lines together with parenteral nutrition solutions.

4. After injection

Patients should void before scanning. This will reduce the background noise as well as the radiation dose to the kidneys and bladder.

Physiological ^{68}Ga-DOTA-conjugated peptide distribution

^{68}Ga-DOTA-conjugated peptides are rapidly cleared from the blood. Arterial elimination of activity is biexponential, and no radioactive metabolites are detected after 4 h in the serum or urine. Maximal tumour activity accumulation is reached 70±20 min after injection. Maximum activity uptake by the kidneys during the time-course after injection averages <50% of the uptake by the spleen. Excretion is almost entirely through the kidneys [18].

SST receptors are expressed by many neuroendocrine and non-neuroendocrine cells of the body, so different organs may be imaged by SST receptor scintigraphy including the liver, spleen, pituitary, thyroid, kidneys, adrenal glands, salivary glands, stomach wall and bowel. The pancreas shows variable uptake of ^{68}Ga-DOTA-conjugated peptides. Though all five subtypes of SST receptors are present in the pancreas, SST receptor 2 predominates and is located in the islets. Accumulation of islets in one pancreatic region (most frequently the pancreatic head) may mimic focal tumour disease in the pancreas. Prostate gland and breast glandular tissue may show diffuse low-grade ^{68}Ga-DOTA-conjugated peptide uptake.

Preparation of ^{68}Ga-DOTA-conjugated peptides

Currently neither ^{68}Ge/^{68}Ga generators nor DOTA-conjugated peptides have marketing authorization and therefore have to be prepared taking into account national regulations and good radiopharmaceutical practices (GRPP) as outlined in specific EANM guidelines [37, 38]

Currently different types of ^{68}Ge/^{68}Ga generator are used, all of them providing ^{68}Ga in strongly acidic hydrochloric acid solutions (0.05–1 *N* HCl). For radiolabelling of DOTA-conjugated peptides different techniques have been developed and are used, usually as semiautomated or fully automated systems. Either they are based on prepurification and concentration of the generator eluate using and anion-exchange [39, 40] or cation-exchange technique [41, 42], or they use a fraction of the generator eluate directly for radiolabelling [43, 44]. Radiolabelling is performed using a suitable buffer at elevated temperature followed by chromatographic purification of the radiolabelling solution using a C-18 cartridge and an appropriate aseptic formulation. The method employed must ensure that the level of ^{68}Ge in the final preparation is lower than 0.001% of the ^{68}Ga radioactivity.

Quality parameters to be tested may vary depending on the technique applied and are currently being defined in a monograph of the European Pharmacopoeia for ^{68}Ga-DOTA-TOC (^{68}Ga-edotreotide injection). Quality control protocols must include tests for radionuclide purity, radiochemical purity (HPLC, TLC), chemical purity (buffer, solvents), and sterility and endotoxin testing using validated methods.

PET/CT scanner quality control

A strict quality control programme should be routinely performed according to the rules of each country, as stated in Council Directives 97/43/ EURATOM.

Image acquisition

Data are acquired using a dedicated PET/CT scanner, preferably using a tomograph capable of 3-D mode acquisition. The timing of image acquisition ranges between 45 90¯min after injection and varies depending on the analogue used. There is no generally accepted acquisition time in the literature, but according to the experience of the centres, best results are achieved with image acquisition at 60¯min. The acquisition comprises a whole-body scan (from the head to middle of the upper leg).

Images should be reconstructed using the iterative reconstruction algorithm implemented in the system and with the system settings. Reconstruction may be performed with or without time of flight information, depending on the system capabilities. When possible it is recommended that data be acquired and reconstructed with time of flight information. Reconstructions should include all regular corrections, such as normalization, (CT-based) attenuation correction, dead time, decay correction and, preferably, model-based scatter correction [45]. During reconstruction resolution recovery may be applied. However, as ‘ring’ artefacts (Gibbs oscillations) have been observed when applying resolution recovery, images without resolution recovery should also be generated and reviewed.

Image analysis

Normal biodistribution and abnormal accumulations should be visually evaluated by a nuclear medicine physician. Tracer accumulation in structures that do not take up the tracer physiologically, or accumulations higher than background activity, can be considered to be pathological. Clearly demarcated findings with higher tracer uptake as compared to the liver uptake are classified as definitely positive for enhanced receptor expression, and thus indicative of malignancy. Linear, nonfocal intestinal uptake with

moderate intensity is considered nonpathological. The pancreas may show variable physiological tracer uptake, with focal areas of uptake, most frequently in the pancreatic head.

Interpretation criteria

In the evaluation of ^{68}Ga-DOTA-conjugated peptide PET/CT studies, the following issues should be taken into consideration:

- The clinical question raised in the request for ^{68}Ga-DOTA-conjugated peptide PET/CT imaging.
- The clinical history of the patient; recent biochemical test results.
- Knowledge of the physiological tracer distribution.
- Anatomical localization of the ^{68}Ga-DOTA-conjugated peptide uptake with corresponding fused CT images; correlation with other imaging modalities (CT, MRI) is strongly recommended.
- Intensity of the ^{68}Ga-DOTA-conjugated peptide uptake (can be expressed semiquantitatively).
- ^{68}Ga-DOTA-conjugated peptides may show variable sensitivity in different tumour types, with respect to tumour histology, expression and density of SST receptors and the site and size of the lesion(s).
- Causes of false-negative results.
- Causes of false-positive results.

Reporting

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

The report should describe:

1. The procedure (^{68}Ga-DOTA-conjugated peptide administered activity, timing of imaging, area imaged).
2. Findings (site and size of the lesion(s), uptake intensity, etc.).
3. Comparative data (the findings should be related to previous PET/CT scans performed with the same tracer, to ^{18}F-FDG PET/CT, if performed, or to the results of other imaging modalities, when appropriate).
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). Additional diagnostic examinations or an adequate follow-up should be suggested, when required.

Sources of error

- Intense accumulation of radioactivity is seen in the spleen (and accessory spleens if present), kidneys and pituitary. Accumulation in the liver can be compared to the intensity in the spleen. The thyroid and salivary glands are faintly visible.
- Additionally, variable tracer uptake is frequently found in the pancreas due to the physiological presence of SST receptor 2.
- Contamination of clothes and/or skin with urine may cause false-positive images.
- Octreotide therapy or the endogenous production of SST (by the tumour) may interfere with tumour detection (reducing or enhancing tumour detectability).
- Variable tumour differentiation and heterogeneous expression of SST receptor subtypes may influence the affinity for ^{68}Ga-DOTA-conjugated peptides and thereby the diagnostic performance.
- Positive findings on ^{68}Ga-DOTA-conjugated peptide PET/CT reflect increased density of SST receptors rather than malignant disease. Uptake is not only specific for malignant tumours. Positive results require evaluation of the possibility that other diseases characterized by a high SST status, e.g. meningioma, activated lymphocytes at sites of inflammation.

Disclaimer The EANM has written and approved guidelines to promote the use of high-quality nuclear medicine procedures. 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 specialized 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, the guidelines cannot be rigidly applied.

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