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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This guideline summarizes the views of the Oncology C 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

Key words: PET - Tumour imaging - Procedure Guidelines – Peptides - Neuroendocrine tumours - Indications
Aim
The aim of this guideline 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 somatostatin receptors. It should not be regarded as the only approach to visualise tumours expressing SST receptors or as exclusive of other imaging modalities useful to obtain comparable results. The corresponding guidelines of $^{111}$In-pentetreotide scintigraphy imaging have been considered and partially integrated with this text [1,2]. The same has been done with the relevant and recent literature on this field and the final result has been discussed by distinguished experts.

Background information and Definitions
The rationale for the employment of $^{68}$Ga-DOTA-conjugate peptides for the assessment of SST receptor expressing tumours relies in the high affinity of these compounds for somatostatin receptors [3-5]. Somatostatin (SST) is a small, cyclic neuropeptide that is present in neurones 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) constitute a heterogeneous group of neoplasms, arising from endocrine cells within glands (adrenal medulla, pituitary, parathyroid) or from endocrine islets in the thyroid, the pancreas, the respiratory and gastrointestinal tract. The majority of NETs express SST receptors, so they can be effectively targeted and visualised with radiolabeled SST analogues in vivo [5-12]. Scintigraphy with radiolabeled SST analogues, first with an I-123 label and subsequently with an In-111 and Tc-99m label, has proven useful in diagnosing SST-receptor positive tumours [4-12]. The detection rate was reported to be between 80% and 100% in different studies. This method also shows the content of SST receptors which might indicate efficacy for treatment with Octreotide or other SST analogues. Furthermore, there is evidence of a correlation between SST receptor expression and prognosis, since patients with NETs showing a positive profile on the scan have a better response to treatment with SST analogues [13,14]. 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 sub-optimal physical resolution of the used isotopes for SPECT imaging [15,16].

More recently, PET with $^{68}$Ga-DOTA-conjugate peptides ([$^{68}$Ga-DOTA$^0$-Tyr$^3$]octreotide ($^{68}$Ga-DOTA-TOC, $^{68}$Ga-edotreotide), [$^{68}$Ga-DOTA$^0$-1Na$^+$]octreotide ($^{68}$Ga-DOTA-NOC), [$^{68}$Ga-DOTA$^0$-Tyr$^3$]octreotate ($^{68}$Ga-DOTA-TATE) ) has brought about dramatic improvements in spatial resolution and is increasingly being used in specialised centres [17,18]. Although $^{68}$Ga-DOTA-TOC, $^{68}$Ga-DOTA-NOC and $^{68}$Ga-DOTA-TATE can all bind to SST receptor 2, they present different affinity profile for other SST receptor subtypes [3]. In particular, $^{68}$Ga-DOTA-NOC shows also a good affinity for SST receptor 3 and 5, $^{68}$Ga-DOTA-TOC binds also to SST receptor 5 (although with lower affinity than DOTA-NOC). $^{68}$Ga-DOTA-TATE presents 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-DOTATATE. 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 [15,16], and provides prognostic information [19].

**Tumours that may be visualised with $^{68}$Ga-DOTA-conjugated peptides PET/CT include:**

Tumours, with high expression of receptors [20-27]

- Gastro-entero-pancreatic tumours (GEP) (e.g.: carcinoids, gastrinoma, insulinoma, glucagonoma, VIPoma, etc.), functioning and non functioning
- Sympatho-adrenal system tumours (phaeochromocytoma, paraganglioma neuroblastoma and ganglioneuroma)
- 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 [28,29]

Clinical Indication
The primary indication of $^{68}$Ga-DOTA-conjugate peptides PET/CT is the imaging of NETs, which usually express high density of SST receptors. Less frequently it can be used in non-NET imaging, particularly if treatment with radiolabeled therapeutic SST analogues is considered. $^{68}$Ga-DOTA-conjugate peptides PET/CT cannot be considered as the first-choice functional modality in management of patients with non-NETs, except for the determination of SST receptor status.

In the management of NETs $^{68}$Ga-DOTA-conjugate peptides PET/CT is used to:
- localise primary tumours and detect sites of metastatic disease (staging) [20-27, 30-32]
- follow-up of patients with known disease to detect residual, recurrent or progressive disease (restaging) [20-27, 30-32]
- determine SST receptor status (patients with SST receptor-positive tumors are more likely to respond to Octreotide therapy) [33, 34]
- select patients with metastatic disease for SST receptor radionuclide therapy (with $^{177}$Lu or $^{90}$Y-DOTA-peptides) [33, 34]
- monitor the response to therapy (surgery, radiotherapy chemotherapy or SST receptor radionuclide therapy) [34]
The sensitivity of $^{68}\text{Ga}}$-DOTA-conjugate peptides PET/CT is likely to vary among tumour types, depending on the density of SST receptors. There are no data suggesting that $^{68}\text{Ga}}$-DOTA-conjugate peptides are useful for dosimetry. The sensitivity of $^{68}\text{Ga}}$-DOTA-conjugate peptides PET/CT 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 or may 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 of radiation in the milk will not result in a radiation dose to the child greater than 1 mSv.
- The ionising radiation from $^{68}\text{Ga}}$-DOTA-conjugate peptides 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 $^{111}\text{In}}$-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 contraindicated) to avoid possible SST receptor blockade; however there are even literature reports of improved tumor-to-background ratios, following pre-treatment with non-radioactive Octreotide. The time interval between interruption of therapy and $^{68}\text{Ga}-
DOTA-conjugate peptides PET/CT depends on the type of drugs used: one
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 centers
are not requiring Octreotide withdrawal before PET scanning.

- No need for fasting before injection

2) Pre-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)
- other imaging modalities’ results (CT, MRI, US, X-rays)
- history of recent biopsy, surgery, chemotherapy, radiotherapy or radionuclide
  therapy
- history of recent SST analogues (Octreotide) therapy.

3) $^{68}$Ga-DOTA-conjugate peptides (DOTA-TOC, DOTA-NOC, DOTA-TATE) administered activity

- The radiopharmaceutical should be administered using an indwelling catheter
to avoid any extravasation.

- The activity of 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. 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.
For the aforementioned reasons the following activity for $^{68}$Ga-DOTA-TOC,
$^{68}$Ga-DOTA-NOC, $^{68}$Ga-DOTA-TATE should be considered only as a general
indication, based on literature data and current experience.

- The activity administered ranges from 100 to 300 MBq, also depending on the
  PET tomograph characteristics. The recommended activity to obtain a good
  image quality is at least 100 MBq. 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 the spleen followed by kidneys and bladder.

- Definitive dosimetric data for $^{68}$Ga-DOTA-TOC, DOTA-NOC and DOTA-TATE are not yet available.
- The amount of $^{68}$Ga-DOTA-conjugate peptides (DOTA-TOC, DOTA-NOC, DOTA-TATE) injected should be below 50 µg (in discussion in PharmEur); this amount is not expected to have any clinically significant pharmacological effect. The radiopharmaceutical should not be injected into intravenous lines together with solutions for parenteral nutrition.

4) Post-injection

Patients should void before scanning. Elimination of the extra fluid intake will help to flush out unbound labelled DOTA-conjugate peptides and non-peptide-bound $^{68}$Ga by glomerular filtration. This will reduce the background noise as well as the radiation dose to kidneys and bladder.

**Physiological $^{68}$Ga-DOTA-conjugate peptides distribution**

$^{68}$Ga-DOTA-conjugate peptides are rapidly cleared from the blood. Arterial activity elimination is bi-exponential and no radioactive metabolites are detected within 4 h in serum and urine. Maximal tumour activity accumulation is reached 70+/-20 min post-injection. Kidney uptake averaged <50% compared with spleen uptake. Excretion is almost entirely through the kidneys [17]. 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, spleen, pituitary, thyroid, kidneys, adrenal glands, salivary glands, stomach wall, bowel.

The pancreas shows variable uptake of $^{68}$Ga-DOTA-conjugate peptides. Though all 5 subtypes of SST receptors are present in the pancreas, the SST subtype 2 receptor is preferably found and is located in the islets. Accumulation of islets in one pancreatic region (more 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-conjugate peptides uptake.
Preparation of $^{68}$Ga-DOTA-conjugate peptides:

Currently neither the $^{68}$Ge/$^{68}$Ga-generators nor the DOTA-conjugated peptide have a marketing authorization and therefore have to be prepared taking into account national regulations and Good Radiopharmaceutical Practices (GRPP) as outlined in specific EANM guidelines [35, 36].

Currently different types of $^{68}$Ge/$^{68}$Ga-generators are being used, all of them providing $^{68}$Ga in strongly acidic hydrochloric acid solutions (0.05-1NHCl). For radiolabelling DOTA-conjugated peptides different techniques have been developed and are being employed, usually using semi- or fully automated systems. They are either based on prepurification and concentration of the generator eluate using an anion-exchange [37, 38] or cation-exchange technique [39, 40], or using a fraction of the generator eluate directly for radiolabelling [41, 42]. Radiolabelling is performed using a suitable buffer at elevated temperature followed by purification of the radiolabelling solution using a C-18 cartridge and appropriate aseptic formulation. Either method employed must ensure that the level of germanium-68 in the final preparation is lower than 0.001 per cent of the gallium-68 radioactivity.

Quality parameters to be tested may vary dependent on the technique applied and are currently being defined within a monograph of the European Pharmacopeia for $^{68}$Ga-DOTA-TOC(Gallium- ($^{68}$Ga) edotreotide injection). Quality control protocols must include tests for radionuclidic purity, radiochemical purity (HPLC, TLC), chemical purity (buffer, solvents) as well as 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 the Council Directives 97/43/ EURATOM.
**Image acquisition**

Data acquisition is performed by means of a dedicated PET/CT scanner, preferably using a tomograph capable of 3D mode acquisition. The timing for images acquisition ranges between 45 minutes after injection and 90 minutes and varies on the basis of the different analogue that is used. There is not a univocal reference in literature, but according to the experience of the centres, best results are achieved with image acquisition preferably at 45 minutes for $^{68}$Ga-DOTA-TATE and 60-90 minutes for $^{68}$Ga-DOTA-TOC or –NOC.

The acquisition is performed as a whole body scan (from head to middle of the upper leg).

Image reconstruction should be performed by an iterative reconstruction algorithm using the system’s implementation and settings. Reconstructions may be performed with or without time of flight information, depending on the systems capabilities. When possible it is recommended to acquire and reconstruct data with time of flight information. Reconstructions should be performed including all regular corrections, such as normalisation, (CT based) attenuation correction, dead time, decay correction and, preferably, model based scatter correction [43]. 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 accumulation should be visually evaluated by a nuclear medicine physician.

Tracer accumulation in structures that do not take up the tracer physiologically or accumulation higher than background activity can be considered to be pathological. Clearly demarkated findings with higher tracer uptake as compared to the liver uptake are classified as definitely positive for enhanced receptor expression and thus indicative for malignancy.

Linear, non-focal intestinal uptake with moderate intensity is considered non-pathological.
Pancreas may show variable physiological tracer uptake, with focal areas of uptake, most frequently in the pancreatic head.

**Interpretation criteria**

To evaluate $^{68}$Ga-DOTA-conjugate peptides PET/CT studies, the following issues should be taken into consideration:

- clinical question raised in the request for $^{68}$Ga-DOTA-conjugate peptides PET/CT imaging
- clinical history of the patient, recent biochemical test results
- comprehension of the physiological tracer distribution
- anatomical localisation of the $^{68}$Ga-DOTA-conjugate peptides uptake with corresponding fused CT images; correlation with other imaging modalities (CT, MRI) is strongly recommended
- intensity of the $^{68}$Ga-DOTA-conjugate peptides uptake (can be expressed semi-quantitatively)
- $^{68}$Ga-DOTA-conjugate peptides may show variable sensitivity in different tumour types, with respect to tumour histology, expression and density of SST receptors and 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 patient’s clinical history, type and date of examination, administered activity and route of administration, relevant medications (patient preparation, Octreotide therapy, withdrawal period, chemotherapy, etc.), laboratory and other imaging studies results.

The report should describe:

1. the procedure ($^{68}$Ga-DOTA-conjugate 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 or to $^{18}$FDG PET/CT, if performed, or to 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 of the spleen. The thyroid and salivary glands are faintly visible.
- Additionally, variable tracer uptake is frequently found in the pancreas due to physiological presence of SST subtype 2 receptor.
- 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 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-conjugate peptides and thereby diagnostic performance
- Positive findings on $^{68}$Ga-DOTA-conjugate peptides PET/CT reflects 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 disease characterised by high SST status, e.g. meningeoma, activated lymphocytes at sites of inflammation.
References


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, resource 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.