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GUIDELINES

Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptides and ^{18}F–DOPA

Murat Fani Bozkurt[1] · Irene Virgolini[2] · Sona Balogova[3,4] · Mohsen Beheshti[5,6] · Domenico Rubello[7] · Clemens Decristoforo[2] · Valentina Ambrosini[8] · Andreas Kjaer[9] · Roberto Delgado-Bolton[10] · Jolanta Kunikowska[11] · Wim J. G. Oyen[12] · Arturo Chiti[13] · Francesco Giammarile[14] · Stefano Fanti[8]

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Abstract
Purpose & Methods Neuroendocrine neoplasms are a heterogenous group of tumours, for which nuclear medicine plays an important role in the diagnostic work-up as well as in the targeted therapeutic options. This guideline is aimed to assist nuclear medicine physicians in recommending, performing, reporting and interpreting the results of somatostatin receptor (SSTR) PET/CT imaging using ^{68}Ga-DOTA-conjugated peptides, as well as ^{18}F-DOPA imaging for various neuroendocrine neoplasms.
Results & Conclusion The previous procedural guideline by EANM regarding the use PET/CT tumour imaging with ^{68}Ga-conjugated peptides has been revised and updated with the relevant and recent literature in the field with contribution of distinguished experts.

Keywords Neuroendocrine tumours · Neuroendocrine neoplasms · Pet/Ct · ^{68}Ga-DOTATATE · ^{68}Ga-DOTATOC · ^{68}Ga-DOTANOC · ^{18}F–DOPA · ^{18}F–FDG · Thyroid medullary cancer · Pheochromocytoma · Paraganglioma · Foregut-NET · Midgut-NET · Hindgut-NET · Hyperinsulism in infants

Background information and definitions

Neuroendocrine neoplasms (NENs) are a heterogeneous group of diverse neoplasms that originate from cells of neuroendocrine origin in many different organs but more frequently from

✉ Murat Fani Bozkurt
fanibozkurt@yahoo.com

✉ Roberto Delgado-Bolton
rbiolton@gmail.com

1 Hacettepe University Faculty of Medicine Department of Nuclear Medicine, Ankara, Turkey

2 Department of Nuclear Medicine, Medical University Innsbruck, Innsbruck, Austria

3 Department of Nuclear Medicine, Comenius University and St. Elisabeth Oncology Institute, Bratislava, Slovakia

4 Department of Nuclear Medicine, Tenon Hospital AP-HP & Université Pierre et Marie Curie, Paris, France

5 PET-CT Center, Department of Nuclear Medicine & Endocrinology, St. Vincent's Hospital, Linz, Austria

6 Department of Nuclear Medicine, Paracelsus Medical University, Salzburg, Austria

7 Department of Nuclear Medicine, PET Center and Medical Physics and Radiology, Santa Maria della Misericordia Hospital, Rovigo, Italy

8 Department of Experimental, Diagnostic and Specialty Medicine-DIMES, University of Bologna, Bologna, Italy

9 Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, National University Hospital & University of Copenhagen, Copenhagen, Denmark

10 Department of Diagnostic Imaging (Radiology) and Nuclear Medicine, San Pedro Hospital and Centre for Biomedical Research of La Rioja (CIBIR), Logroño, Spain

11 Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland

12 Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK

13 Nuclear Medicine Department, Humanitas University, Rozzano, MI, Italy

14 Nuclear Medicine, University of Lyon, Lyon, France

the gastrointestinal tract and the lungs. Less common locations include thymus and other organs with endocrine function such as adrenal medulla, pituitary, parathyroid and thyroid.

The majority of NENs express somatostatin receptors (SSTR), which can be used as targets for radionuclide imaging and therapy. Somatostatin is a small cyclic neuropeptide that is found in neurons and endocrine cells and has a high density in the brain, peripheral neurons, endocrine pancreas and gastrointestinal tract [1–10]. Since the metabolic stability of naturally occurring somatostatin is very low, synthetic analogues with much more stability have been developed [1, 11].

Scintigraphy with radiolabeled somatostatin analogues, first with ^{123}I labelling and followed by ^{111}In and ^{99m}Tc labelling, has been effectively used for the work-up of SSTR-positive NEN patients with a recorded detection rate between 50% and 100% in different studies [1–11]. Both in planar and SPECT (or SPECT/CT) images, SSTR scintigraphy presents some limitations that may decrease the diagnostic efficacy. This is mostly due to high physiological uptake such as in the liver as well as the lack of detection of smaller lesions because of the suboptimal physical characteristics of the radiopharmaceuticals and the lower resolution of gamma cameras [12, 13].

PET imaging with ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-conjugated peptides, which are targeted to SSTR, has brought a new vision with regard to spatial resolution and patient comfort due to earlier and shorter acquisition times compared to SPECT radiopharmaceuticals. The most commonly used ^{68}Ga-DOTA-conjugated peptides are[^{68}Ga-DOTA^{0} -Tyr^{3}] octreotide (^{68}Ga-DOTA-TOC, ^{68}Ga-edotreotide), [^{68}Ga-DOTA^{0}-^{1}NaI^{3}]octreotide (^{68}Ga-DOTA-NOC) and [^{68}Ga-DOTA^{0} -Tyr^{3}]octreotate (^{68}Ga-DOTA-TATE) [14–16]. Although all these radiopeptides bind to SSTR2, each has different affinity profiles for other SSTR subtypes [17] (Table 1). Along with highest affinity to SSTR2,^{68}Ga-DOTA-NOC also shows a high affinity to SSTR3 and SSTR5, ^{68}Ga-DOTA-TOC binds also to SSTR5 (with lower affinity compared to DOTA-NOC) while ^{68}Ga-DOTA-TATE predominantly binds to SSTR2. Finally,^{68}Ga-DOTA-lanreotide binds to SSTR2 and SSTR5 [18]. Recently, also ^{64}Cu-DOTA-TATE has been used in NEN patients and was found superior to SPECT-based somatostatin receptor imaging [19]. However, with the above-mentioned tracers, it should be kept in mind that in most NEN, SSTR2 is the receptor subtype predominantly expressed [20]. Although these abovementioned radiopeptides function as receptor agonists to SSTR, recently some other radiopeptides with antagonist effects on SSTR have been introduced. Limited data on SSTR antagonist radiopeptides especially for PET applications exist, which might more efficiently localise NENs due to imaging higher number of binding sites on tumours (practically all the subtypes) and more stable binding [21].

SSTRs are not only targets for radionuclide imaging but also serve for radionuclide therapy of NENs. Confirmation of receptor affinity with diagnostic imaging can indicate the potential for peptide receptor radionuclide therapy (PRRT). PRRT using receptor agonist or antagonist, on the basis of the theranostic approach has been accepted as an effective treatment option for NEN, since it has been introduced. ^{68}Ga as a positron emitter radionuclide can only be used for diagnostic imaging. For therapy, beta-emitters such as ^{177}Lu and ^{90}Y are the major radionuclides that can be used for PRRT.

Many papers in the literature report the relevant role of PET/CT imaging with^{68}Ga-DOTA-conjugated peptides in the clinical management of NENs. According to receptor avidity and affinity, patients can be guided to PRRT. The therapeutic radionuclide decision with the appropriate radiopeptide should be done on the basis of some factors such as the tumour size and location of the disease, which can easily be detected by pre-therapy diagnostic PET imaging [22].

Along with SSTR, NENs can be imaged by using other molecular and metabolic targets due to their neuroendocrine functional features. Most widely studied for this application has been 6-l-^{18}F-fluoro-dihydroxyphenylalanine (^{18}F–DOPA). Many papers in the literature report the higher accuracy of ^{18}F–DOPA for imaging well differentiated NENs as compared to conventional imaging and gamma camera scintigraphy. Currently, the main clinical indication for NEN imaging with ^{18}F–DOPA (also considering its relatively difficult availability and costly synthesis) is represented by tumours with low/variable SSTR expression, such as neuroectodermal tumours [23]. Furthermore, since several types of malignant and nonmalignant lesions may show variable expression of SSTR, ^{18}F–DOPA, as a tracer of the catecholamine metabolic pathway, may be helpful in the characterisation of lesions as attributable to medullary thyroid cancer, jejuno-ileal (midgut) NEN, pheochromocytoma, neuroblastoma or paraganglioma

Table 1 Affinity profiles of different SSTR analogues

Peptide	Sstr1	Sstr2	Sstr3	Sstr4	Sstr5
68Ga-DOTATOC	>10.000	2.5 ± 0.5	613 ± 140	>1000	73 ± 21
68Ga-DOTATATE	>10.000	0.2 ± 0.004	>1000	300 ± 140	377 ± 18
68Ga-DOTANOC	>10.000	1.9 ± 0.4	40.0 ± 5.8	260 ± 74	7.2 ± 1.6

The table lists the values for the inhibitory constant (nmol/L) for ^{68}Ga-conjugated peptides. The IC50 value indicates the concentration when 50% of binding is inhibited.

in patients with doubt for synchrone/metachrone metastatic malignancy (e.g., breast cancer). Finally, even if ^{18}F–DOPA has no theranostic role, during the evaluation prior to treatment with somatostatin analogues, it may identify lesions with only weakly or not expressing SSTR and predict poor or no response to these lesions. Similarly, in the post-therapeutic setting, ^{18}F–DOPA may be helpful in the identification of new lesions (i.e., disease progression).

Furthermore, radiolabelled peptide analogues targeting the cholecystokinin-2 receptor have been also described for NEN imaging. Initial clinical studies with ^{99m}Tc and ^{111}In labelled gastrin analogues showed very promising results in patients with MTC [24, 25] as well as patients with other NENs [26]. Recently, a new radiolabelled gastrin analogue with very promising characteristics for clinical translation, in terms of high metabolic stability, prolonged tumour uptake and low kidney retention, has been developed and will be studied in patients with metastatic MTC in the near future [27]; however, evidence regarding possible PET-applications is still lacking.

^{18}F-2-fluorodeoxyglucose (^{18}F–FDG) PET/CT imaging plays a role not in recognition of disease but has important impact on prognostication of NENs. While most of the low grade highly differentiated NENs show high uptake of radiolabeled SSTR analogues and ^{18}F–DOPA, poorly differentiated and more aggressive NENs show preferential uptake of the glucose analogue. Many reports indicate that, when positive, ^{18}F–FDG is prognostic, identifying cases with a more aggressive disease and worse prognosis [28].

According to eighth edition of the AJCC (*American Joint Committee on Cancer*) 2017 classification, NENs are divided into neuroendocrine tumours (NET) as NET Grade1, NET Grade 2 and NET Grade 3 and neuroendocrine carcinoma (NEC) as a separate group (Table 2) [29]. This classification takes into account the proliferation marker Ki-67 index without the mitotic index of the tumour, in contrast to previous World Health Organisation (WHO) 2010 classification.

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

– Tumours with high expression of somatostatin receptors [16, 30–36].

- Gastro-entero-pancreatic tumours (GEP) functioning and non-functioning (e.g.:gastrinoma, insulinoma, glucagonoma, VIPoma, etc.)
- Lung NENs
- Sympatho-adrenal system tumours (e.g., paraganglioma)
- Meningioma

– Tumours with low or varying expression of receptors [37, 38].

- Breast carcinoma
- Melanoma
- Lymphoma
- Prostate carcinoma
- Non-small cell lung cancer
- Head and neck cancer
- Sarcoma
- Renal cell carcinoma
- Differentiated thyroid carcinoma
- Astrocytoma

– Tumours with neuroendocrine/neuroectodermal features that may be visualised with ^{18}F–DOPA PET/CT include [31, 39–42]:

- Jejuno-ileal(midgut) NENs
- Pheochromocytoma
- Paraganglioma
- Neuroblastoma
- Medullary thyroid cancer

– Other tumours/tumour-like conditions with high ^{18}F–DOPA uptake include:

- Brain tumours
- Beta cell hyperplasia (especially for the indication of congenital hyperinsulinemichypoglycemia)

– Tumours with neuroendocrine features that show high ^{18}F–FDG uptake:

- Neuroendocrine carcinomas (NECs)
- Neuroendocrine neoplasms (NENs) with high histologic grade or G2 and G3 NETs with suspected aggressive behaviour
- Medullary thyroid cancer (MTC)
- Mixed adenoneuroendocrine cancers (MANEC)
- Synchrone/metachrone non-NEN malignancies

Clinical indications of PET/CT imaging with ^{68}Ga-labelled somatostatin analogues

The primary indication of ^{68}Ga-DOTA-conjugate peptides PET/CT imaging is localisation and characterisation of NENs, which usually express high density of SSTR.

Less frequently it can be used in non-NEN imaging, particularly if treatment with radiolabeled therapeutic somatostatin analogues is considered. ^{68}Ga-DOTA-conjugate peptides

Table 2 Classification of NENs according to AJNCC 2017 [29]

Neuroendocrine Neoplasm (NEN)			
NEN with Ki-67 < 20%		NEN with Ki-67 > 20%	
NET G1 Neuroendocrine tumours low grade Ki-67 < 3%	NET G2 Neuroendocrine tumours well differentiated Ki-67 3%–20%	NET G3 Neuroendocrine tumours well differentiated Ki-67 21%–55%	NEC Neuroendocrine carcinoma with Ki-67 > 21%, usually > 55% - large cells - small cells

PET/CT cannot be considered as the first-choice functional modality in the management of patients with non-NENs, except for the determination of SSTR status.

Based on available bibliographic evidence, the following indications for PET/CT imaging with ^{68}Ga-labelled somatostatin analogues are documented:

- Detection of the primary occult neuroendocrine tumour when a metastasis of an unknown primary neuroendocrine tumour has been demonstrated or when the serum concentration of a specific tumour marker is increased with no evidence of a primary tumour at conventional imaging modalities.
- Characterisation of a bronchial mass as neuroendocrine tumours when other diagnostic modalities were not conclusive.
- Characterisation, staging, detection in case of biochemical recurrence and restaging of neuroendocrine tumours of the foregut, including in the thymus or the bronchi.
- Characterisation, staging, detection in case of biochemical recurrence and restaging of jejuno-ileal (midgut) neuroendocrine tumours, when ^{18}F–DOPA is not available or PET/CT imaging with ^{18}F–DOPA is non-conclusive.

In the management of NENs ^{68}Ga-DOTA-conjugate peptides PET/CT is used for

- Diagnosis and staging: Localise primary tumours and detect sites of metastasis (staging) [32–38, 43–45].
- Re-staging: Follow-up of patients with known disease to detect residual, recurrent or progressive disease (restaging) [32–38, 43–46].
- Prognosis: Determine SSTR status (patients with SSTRpositivetumors are more likely to respond to targeted somatostatin analogues therapy) [15, 42, 44].
- Management decisions: Select patients with metastatic disease for SSTR radionuclide therapy (with ^{177}Lu or ^{90}Y–DOTA-peptides) [44, 47].
- Monitor the response to therapy (surgery, radiotherapy, chemotherapy or PRRT) [48].

The sensitivity of ^{68}Ga-DOTA-conjugate peptides PET/CT is likely to vary among tumour types, depending on the density of SSTR receptors. Due to the short half-life of ^{68}Ga, conjugated peptides cannot be used for dosimetry, which is usually derived from ^{177}Lu-DOTA-labelled peptides. The sensitivity of ^{68}Ga-DOTA-conjugate peptides PET/CT may theoretically be reduced in patients receiving therapeutic doses of somatostatin analogues such as octreotide, but this issue still needs to be clarified [49].

On empirical grounds prior PET with ^{68}Ga-DOTA-conjugated peptides, it has been recommended to discontinue therapy with somatostatin analogues (when possible and not contraindicated) to avoid possible SSTR blockade [50]. However, there are literature reports of an improved tumour/non-tumour ratio, following pre-treatment with somatostatin analogues as a consequence of non-saturability of SSTR expressed by malignant cells in contrast to SSTR expressed by non-malignant ones [51, 52].

If discontinuation is undertaken, it has been reported that the time interval between interruption of therapy and ^{68}Ga-DOTA-conjugated peptides PET/CT depends on the type of somatostatin analogue 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 some centres do not require octreotide withdrawal before PET examination. Some centres suggest that the best option is to perform the PET/CT study just prior to the scheduled monthly dose of long-acting octreotide [50].

However, taken together there is no clear evidence that discontinuation of somatostatin analogues prior to PET imaging with ^{68}Ga-DOTA-conjugated peptides is necessary.

Indications for ^{18}F–DOPA PET/CT for NENs

PET with ^{18}F–DOPA provides a functional approach of pathologies, organs or tissues, where enhanced intracellular

transport and decarboxylation of the amino acid DOPA is the diagnostic target.

For functional imaging of NEN, ^{18}F–DOPA is approved in several EU countries in following indications:

– Diagnosis

- Diagnosis and localisation of glomus tumours in patients with a gene mutation of the succinate dehydrogenase D variant
- Localisation of pheochromocytoma and paraganglioma
- Diagnosis and localisation of insulinomas in the case of hyperinsulinism in infants and children

– Staging

- Phaeochromocytoma and paraganglioma
- Well-differentiated neuroendocrine tumours of the digestive tract

– Detection in case of reasonable suspicion of recurrences or residual disease

- Phaeochromocytoma and paraganglioma
- Medullary thyroid cancer with elevated serum levels of calcitonin
- Well-differentiated NETs of the digestive tract
- Other endocrine digestive tumours when somatostatin receptor scintigraphy is negative.

Indications for ^{18}F–FDG PET/CT for NENs

- Localisation of NECs and high-grade poorly-differentiated NETs with aggressive behaviour.
- Prognosis
- Localisation of synchrone/metachrone non-NEN malignancy

The proposed diagnostic strategy with the use of abovementioned radiopharmaceuticals that are currently available is tabulated in Table 3 based on different NEN types.

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 after elapsing of seven physical half-lives of radionuclide in a radiopharmaceutical, 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}Ga-DOTA-conjugate peptides administration must be carefully evaluated in subjects less than 18 years of age. However, the dosimetry of ^{68}Ga- somatostatinanalogues is more favourable than that of ^{111}In-pentetreotide.

It has been recommended to temporarily withdraw somatostatin analogue therapy (when possible) to avoid possible SSTR blockade (see patient preparation). In some patients the withdrawal of therapy might not be tolerated [50–52].

Pre-examination procedure for ^{68}Ga-conjugate peptides PET imaging

1) Patient preparation

- The physician or the technologist should give the patient a detailed explanation and information about the procedure.
- It has been advocated by some authors to withdraw “cold” octreotide therapy (when possible and not contraindicated) to avoid possible SSTR blockade. The time interval between interruption of therapy and ^{68}Ga-DOTA-conjugate peptides PET/CT depends on the type of drugs used: 1 day is suggested for short-lived molecules and at least 3–4 weeks for long-acting analogues [50–52].
- No need for fasting before injection.

2) Pre-injection

The nuclear medicine physician should consider all the following information useful for an optimal interpretation of the study:

- 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, (including tumour grading and ki-67), surgery, chemotherapy, radiotherapy or radionuclide therapy
- History of recent somatostatin analogue therapy and of PRRT

3) Administration of ^{68}Ga-DOTA-conjugate peptides (DOTA-TOC, DOTA-NOC, DOTA-TATE)

Table 3 Proposed diagnostic strategy based on the NEN type

Type of NEN	Place in diagnostic strategy (I-II-III)*		
	^{68}Ga-somatostatin analogue	*^{18}F–DOPA*	*^{18}F–FDG*
Medullary thyroid cancer	III mainly when treatment with SST analogues is an option	In patients with high serum calcitonin levels: I In patients with high serum CEA levels II	In patients with high serum calcitonin levels II In patients with high serum CEA levels I
Foregut NET	I	Not indicated	I
Midgut NET	I	I	II
Hindgut-NET	II	II	I
Pheochromocytoma	II/III	With SDHD mutation I With SDHB mutation II-	With SDHD mutation II With SDHB mutation I
Paraganglioma	Head and neck I Abdomen/pelvis II	Head and neck II Abdomen/pelvis I	Head and neck III Abdomen/pelvis III
CUP NET	If suspected primary foregut I	İf suspected primary midgut I	To localise the primary tumour and eventual non-NET malignancy I
Neuroblastoma		I	Older age, advanced stages or MYCN amplification I
Hyperinsulinism in infants and in children		I	

CUP: carcinoma of unknown primary

*I: The first choice proposed

II: The second choice proposed

III: The third choice proposed

- The radiopharmaceutical should be administered using an indwelling catheter to avoid any extravasation.
- 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. 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 200 MBq, also depending on the PET scanner technical characteristics and patient body weight. 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 [53]. The organ that 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 available in the literature, and the mean effective dose is 0.023, 0.025, and 0.0257 mSv/MBq, respectively, in several dosimetric studies [54–56].
- The amount of DOTA-conjugate peptides (DOTA-TOC, DOTA-NOC, DOTA-TATE) injected should be below 50 μg; 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.

Pre-examination procedure for ^{18}F–DOPA PET imaging

1) Patient preparation

- The physician or the technologist should give the patient a detailed explanation and information about the procedure.
- The oral premedication by the decarboxylase inhibitor carbidopa (L-alpha-hydrazino-alpha-methyl-b-3,4-dihydroxyphenyl propionic acid), which was introduced to block the aromatic aminoacid decarboxylase enzyme, is controversial. The posology of carbidopa usually ranges between 100 and 200 mg (or 2 mg/kg of body weight) [57]. Eriksson et al. reported that the pre-treatment with carbidopa led to a 6-fold decrease in renal excretion while the tumour uptake increased three-fold [58]. Concordantly, Timmers et al. [59] reported that, compared with baseline^{18}F–DOPA PET, carbidopa pre-treatment resulted in the detection of three additional lesions in three of 11 patients with pheochromocytoma or extra-adrenal paraganglioma. In contrast, in one infant of the Ribeiro's series the diffuse uptake of ^{18}F–DOPA in the pancreas completely disappeared under carbidopa treatment, while the kidney activity was still present; the patient had histologically proven diffuse abnormal pancreatic cells scattered in the whole pancreas [60]. Similar findings have been reported by Kauhanen et al. in 2008 in two of three adults with insulinoma [61]. These findings do not favour the use of carbidopa in patients with pancreatic tumours since pancreatic physiological uptake disappears, and tumour uptake could also disappear along with this. Carbidopa effect on ^{18}F–DOPA uptake in insulinomas is not fully elucidated. No final consensus has been reached about the usefulness of carbidopa in patients with insulinoma-related hyperinsulinemic hypoglycaemia [62, 63].

Currently, no preparation of carbidopa (without levodopa) is commercially available.

Fasting On an empirical basis, to avoid interaction with aminoacids from food, ^{18}F–DOPA should be administered to patients fasting for a minimum of 4 h without limiting water intake.

Medication withdrawal No special interactions have been reported and no therapeutic discontinuation of F-DOPA is needed.

Posology and time of acquisition According to extensive literature data, the recommended activity of ^{18}F–DOPA for an adult is 2 to 4 MBq/kg (this activity has to be adapted according to the PET scanner technical characteristics and the acquisition mode), administered by direct slow intravenous injection over approximately 1 min [64, 65].

The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card.

To detect foci in the liver, intestine or pancreas area, early "static" images can be acquired starting 5 min after injection, or a "dynamic" acquisition starting right after the injection for 10 min. Whole-body: images are usually acquired 60 min after injection.

Physiological biodistribution of ^{68}Ga-DOTA-conjugate peptides

^{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 [13]. SSTRs 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 five subtypes of SSTR are present in the pancreas, the SSTR2 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 [66]. Prostate gland and breast glandular tissue may show diffuse low-grade ^{68}Ga-DOTA-conjugate peptide physiologic uptake.

Biodistribution of ^{68}Ga-DOTA-conjugate peptides may show some differences depending on the receptor coverage of the individual peptide that is conjugated to the molecule. According to literature data, ^{68}Ga-DOTATATE, which has mainly affinity to SST receptor subtype 2, shows more intense physiological uptake in the pituitary and salivary gland [56], in comparison with that of ^{68}Ga-DOTANOC, with receptor coverage of 2, 3 and 5. Although the receptor subtype coverage of ^{68}Ga-DOTATATE is limited compared to ^{68}Ga-DOTANOC, the lesions showed more intense uptake which result in higher lesion-to-background ratio in ^{68}Ga-DOTATATE imaging compared with ^{68}Ga-DOTANOC [67].

However, there is still a debate in the literature whether uptake pattern differences due to receptor coverage of various radiopeptides significantly affects interpretation of the scans. Some studies state that despite the differences between biodistribution patterns of various radiopeptides mainly due to different receptor subtype affinities, all radiopeptides have comparable diagnostic performance and this difference has no significance with regard to interpretation of the scans. However, there are also some studies stating that SST 2,3,5-specific radiotracer ^{68}Ga-DOTANOC detects significantly more lesions than the SST2-specific radiotracer ^{68}Ga-DOTATATE in patients with gastroenteropancreatic-NENs, although the clinical relevance of this finding has yet to be proven in larger studies [68]. As a result, there are, to our knowledge, no clinically relevant differences, although some studies of comparison reported the superiority of one radiopharmaceutical over the other in very limited sample populations.

Physiological biodistribution of ^{18}F–DOPA

According to a study on biodistribution of ^{18}F–DOPA, which included a cohort of 107 patients, the radiopharmaceutical showed uptake in the basal ganglia (mean SUVmax 2.8, range 1.5–3.6), liver (mean SUVmax 2.2, range 1.1–2.9), the pancreas mainly in the uncinate process (mean SUVmax 5.7, range 2.9–14.1) and less intense in the body–tail region (mean SUVmax 4.1, range 2.1–6.2), adrenal glands (mean SUVmax 1.9, range 0.7–4.3). Very intense and variable uptake was seen in the excretory organs: gallbladder and biliary tract (mean SUVmax 8.5), kidneys (mean SUVmax 4.4), ureters and urinary bladder (mean SUVmax 111) depending on individual elimination timing. In their series, bowel uptake (mean SUVmax 2.3) was an unusual finding and, when seen, presented only mild diffuse uptake. Mild uptake can be also seen in the liver, myocardium, peripheral muscles and in some cases a very faint uptake can be seen in the mammary glands, the oral cavity, the oesophagus, and the bowel. The uptake was mildly variable in the basal ganglia and even less variable in the liver parenchyma. However, greater variability was observed in the pancreas, especially in the uncinate process and in the adrenal glands. Regarding the adrenals, this data showed significant variability in ^{18}F–DOPA uptake [64, 69]. In the literature it is reported that children can present ^{18}F–DOPA uptake in the growth plates [70].

Effect of carbidopa premedication on the biodistribution of ^{18}F–DOPA

The oral premedication by the decarboxylase inhibitor carbidopa, which was introduced to block the aromatic aminoacid decarboxylase enzyme, is controversial and is of less common use than in neurologic indications. The administration of carbidopa increases, the uptake of ^{18}F–DOPA in the basal ganglia, lungs, myocardium and liver and decreases the pancreatic uptake of ^{18}F–DOPA [59]. Physiologic excretion into the ducts of the biliary tract, the gallbladder and the urinary system continues to be seen after carbidopa and no changes were reported. Similar effects of carbidopa premedication are reported in children [70].

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

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) [61]. 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 or cation-exchange technique, or using a fraction of the generator eluate directly for radiolabelling. 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 (^{68}Ge) in the final preparation is lower than 0.001%of the gallium-68 (^{68}Ga) radioactivity. Quality parameters to be tested may vary depending on the technique applied and are currently defined within a monograph of the European Pharmacopoeia for ^{68}GaDOTA-TOC(*Gallium- (^{68}Ga) Edotreotide Injection, No. 2482*). 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. National regulations have to be followed in preparation and QC of these products. A review on production technologies and quality aspects can be found [71, 72].

Recently generators with a marketing authorisation have become available and radiolabelling kits are in the pipeline. This will simplify kit-based preparation of ^{68}Ga-SST analogues potentially reducing the requirements for purification, GMP compliance and quality control.

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 of ^{68}Ga-DOTA conjugate peptides

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

Image interpretation for ^{68}Ga-DOTA conjugate peptides PET/CT

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 demarcated findings with higher tracer uptake as compared to the liver uptake are classified as definitely positive for enhanced SSTR 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 [66].

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

Image interpretation for ^{18}F–DOPA PET/CT

^{18}F–DOPA traces a very specific metabolic process and presents non-specific accumulation only to its excretory pathways. In other normal tissues ^{18}F–DOPA has minimal uptake and therefore provides good lesion-to-background ratios. Patients who are referred for ^{18}F–DOPA PET/CT have already a clinical suspicion of disease based on their clinical record and on biochemical findings or imaging procedures so they present with a very precise clinical indication. Thus, it is helpful to be a priori aware of what is expected to "be seen" (physiologic pattern and variants), what is "looked for" (a paraganglioma, lesions of medullary thyroid cancer or lesions of midgut-NET, etc.), where it should be localised (locoregional relapse or lymph nodes for MTC, adrenals for suspected pheochromocytoma, pancreas for insulinoma), how it would present (usually focal intense uptake that does not follow the physiologic biodistribution) and what could mask its identification (uptake in excretory organs like gallbladder, pancreas and urinary tract).

A larger variability in ^{18}F–DOPA uptake can be seen in the pancreas, especially in the uncinate process that, in some cases, can show very intense uptake. Similarly, uptake by the adrenal glands may be highly variable and this must be taken into consideration to avoid misinterpretation of a normal adrenal as a pheochromocytoma. When ^{18}F–DOPA uptake, even if relatively high, is homogeneous, and usually symmetrical and not associated with morphological alteration on CT imaging, the appearance should be considered as indicating physiological and normal adrenal uptake. No significant or mild diffuse uptake is usually noted in the bowel. As mentioned above, the excretory organs (gallbladder, kidneys and urinary bladder) show a high variability of SUVmax values depending on individual elimination timing and hydration status. The biodistribution data are relatively constant in terms of the intensity of liver uptake. This could be helpful when semi-quantitative analyses based on the lesion-to-background

ratio are needed: for this purpose, the liver uptake could be regarded as a background parameter.

In the evaluation of the whole body ^{18}F–DOPA PET scan any area of focal uptake outside the areas of physiologic distribution of the tracer can be considered as pathological. In suspicion of paragangliomas/pheochromocytomas any nonphysiological extra adrenal focal uptake or asymmetrical adrenal uptake with a concordant enlarged gland or adrenal uptake more intense than that of the liver with a concordant enlarged gland can be considered pathological.

Carbidopa premedication enhances the uptake of ^{18}F–DOPA by paraganglioma lesions and significantly blocks physiologic tracer uptake by the pancreas that can be a potential confounder in the detection of adrenal lesions. Carbidopa premedication in the paediatric population seems to influence ^{18}F–DOPA distribution in the liver and pancreas in a manner similar to that reported in adults: a clear reduction in the abdominal accumulation of ^{18}F–DOPA both to the biliary structures and the excretory system, accompanied by a generalised increase in soft tissue uptake, as well as in the basal ganglia and liver parenchyma.

Reporting of the scans

For both ^{68}Ga-DOTA conjugate peptides and ^{18}F–DOPA PET/CT imaging, 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, CT parameters and dosimetry, relevant medications (patient preparation, previous therapy with cold somatostatin analogues, carbidopa premedication, withdrawal period, chemotherapy, etc.), laboratory and other imaging studies results.

The report should describe

1. The procedure (the type of ^{68}Ga-DOTA-conjugate peptide and its administered activity, the administered activity of ^{18}F–DOPA, acquisition time, duration of imaging, the area imaged).
2. The findings (site and size of the lesion(s), uptake intensity, SUVmax, 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.

Common pitfalls for ^{68}Ga-DOTA conjugate peptides PET/CT

- 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 (mostly) faintly visible. Adrenals also are visible.
- Additionally, variable tracer uptake is frequently found in the head of the pancreas.
- Contamination with urine of clothes and/or skin may cause false positive images.
- Somatostatin analogue such as 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 SSTR may influence the affinity for ^{68}Ga-DOTA-conjugate peptides and thereby diagnostic performance.
- False negative findings may be due to lesion dedifferentiation or small size.
- False positive findings on ^{68}Ga-DOTA-conjugate peptides PET/CT:Uptake is not only specific for malignant tumours but can be encountered in the presence of activated lymphocytes (that can express SRS) at sites of inflammation/infection.

Common pitfalls for ^{18}F–DOPA PET/CT

Intense focal uptake of the tracer in the gallbladder, and in some cases the common bile tract, can mimic an intestinal tumour or an hepatic metastasis by a NEN primary and has already been reported as a possible pitfall [73]. In this case the knowledge of the normal biodistribution of the tracer and its physiological excretion through the biliary route and, of course, the correlative CT images of the PET/CT can easily help the "reader" identify the site of the uptake as physiologic activity in the gallbladder or the biliary path.

Urinary excretion is the major excretion route of the tracer, and it can be the cause of several pitfalls. The intense uptake of the tracer in the kidneys could "mask" a pathologic uptake in the tail of the pancreas (left kidney); the activity in the right kidney interferes less with the head of the pancreas. Moreover, uptake in the kidneys could hide a pathologic uptake of the adrenals, especially in patients with dilatation of the superior caliceal groups or who present just an accumulation of the tracer within the superior intrarenal urinary path. Uptake in the ureters, even if less intense and usually with a "spotting" appearance could resemble pathologic abdominal uptake in the bowel or in lymph nodes. The bladder, even if it presents a very intense accumulation of the tracer, is less interfering

since usually a PET scan starts with an empty bladder. In all cases in addition to the knowledge of the possible physiologic accumulation of the tracer, and always in relation to the clinical suspicion, the low dose CT images for the attenuation correction of the multimodalityPET/CT scanners offer the most important help since they can precisely localise the anatomical counterpart of the uptake. Also in case of interpretative doubts, the tracer (half life of 110 min) offers the possibility to acquire late images after diuretic administration or after ambulation and hydration that could alter the appearance of the uptake and help discriminating between pathologic/physiologic.

The physiologically intense and very variable uptake in the pancreas can lead to two possible pitfalls: on the one hand, uptake in the pancreas, especially in the uncinate process, can be confused as a para-aortic pathologic lesion (false positive) and on the other, pancreas can contain a genuine lesion with the same uptake intensity not identified as pathologic by ^{18}F–DOPA (false negative). Moreover, physiologic pancreatic uptake is a potential limitation of ^{18}F–DOPA PET in the detection of adrenal lesions; in these cases premedication with carbidopa prevents masking of a possible lesion by blocking the pancreatic uptake. Moreover, carbidopa as mentioned before not only "cleans" the vision in the peripancreatic region but also increases the uptake in the lesions, which can be more easily identified.

The utility of ^{18}F–DOPA PET/CT in adult patients with hyperinsulinemic hypoglycemia can be cumbersome, since there are few differences between pathologic or non-pathologic areas of the pancreas which show a very variable physiologic uptake of the tracer. Moreover, premedication with carbidopa could lead to another possible methodological pitfall when considering patients with hyperinsulinemic hypoglycemia since carbidopa (a peripheral AADC inhibitor) decreases the whole pancreatic uptake decreasing also the lesion to background ratio [74]. Disappearance of ^{18}F–DOPA focal pancreatic hot spots has been reported after premedication with carbidopa in patients with hyperinsulinemic hypoglycaemia [60, 70, 74].

Pitfalls related to the pathology

Some possible sources of false-negative results of ^{18}F–DOPA PET/CT can be related to factors such as the small size of the lesion or tumour dedifferentiation. Genetic factors may also affect the ^{18}F–DOPA uptake in paraganglioma. Succinate dehydrogenase B-subunit (SDHB) gene mutations may result in extra-adrenal paraganglioma for which ^{18}F–DOPA PET shows a lower sensitivity than for non-SDHB-related lesions [59]. On the other hand the high specificity of ^{18}F–DOPA PET and PET/CT, explained by the fact that only neuroendocrine cells are able to take up, decarboxylate and store amino acids and their amines, leads to few false-positive ^{18}F–DOPA PET findings.

Koopmans et al. studied prospectively 53 patients with carcinoid tumour, and they recorded a patient-based sensitivity of 100%, region-based of 95% and lesion-based 96% better than CT, SRS and combined CT/SRS, and they do not report any false positive cases [75].

In a meta-analysis on MTC, some authors report that false positive findings with ^{18}F–DOPA are uncommon, on the other hand false, negative results could be probably related to small MTC lesions or to dedifferentiation. In fact, comparative analysis between ^{18}F–DOPA and ^{18}F–FDG have shown better results with ^{18}F–DOPA in terms of sensitivity and specificity. These PET radiopharmaceuticals reflect two different metabolic pathways and seem to have a complementary role in recurrent MTC; a higher ^{18}F–DOPA uptake is related to a higher degree of cell differentiation, whereas a higher ^{18}F–FDG uptake is related to a poor differentiation/dedifferentiation. Based on literature findings, the diagnostic performance of ^{18}F–DOPA in recurrent MTC improved in patients with higher serum calcitonin levels [76, 77]. High levels of calcitonin and negative ^{18}F–DOPA PET could depend on the small size of the recurrence. High levels of CEA and negative ^{18}F–DOPA PET could depend on dedifferentiation of the tumour and its inability to uptake ^{18}F–DOPA, so ^{18}F–FDG would be the radiopharmaceutical of choice.

Technical pitfalls

PET/CT represents a major technologic advance, consisting of two complementary modalities, which provide both functional and anatomic information and whose combined strength tends to overcome their respective weaknesses. With combined PET/CT, the superimposition of the precise structural findings provided by CT allows an accurate correlation of the radiotracer activity seen at PET with the correct anatomic or pathologic equivalent. When attenuation correction is based on the CT images, there is a potential risk of overestimating the true activity of the tracer such as in case of photopenic areas corresponding to high density structures at CT (metallic implants, surgical clips, barium) [78].

Another possible pitfall can be caused by misregistration between PET and CT images, thus a superimposition of radiotracer activity on the wrong anatomic structure seen at CT, which can be due to breathing, patient motion, bowel motility, etc., and can cause false-positive or false-negative PET findings.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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