

⁶⁸Ga-labelled peptides for diagnosis of gastroenteropancreatic NET

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Abstract In the past few years, the introduction of novel PET tracers labelled with ⁶⁸Ga has changed the diagnostic approach to neuroendocrine tumours (NET) in specialized centres. Although somatostatin analogue tracers labelled with ¹¹¹In have represented the gold standard imaging modality for NET detection in past decades, the advantages offered by both labelling somatostatin analogues with ⁶⁸Ga and using PET/CT tomography for image acquisition, account for the increasing use of these tracers in clinical practice. There are an increasing number of reports of the higher accuracy of ⁶⁸Ga-DOTA peptide PET/CT for the detection of NET lesions as compared to morphological imaging procedures and somatostatin receptor scintigraphy. Moreover, the use of ⁶⁸Ga-DOTA peptides offers the possibility to noninvasively evaluate NET cells for the presence of somatostatin receptor expression, with direct therapeutic implications. Several practical advantages also favour the use of ⁶⁸Ga-DOTA peptides including the relatively easy and economic synthesis process and the fact that ⁶⁸Ga labelling can be performed in centres without an on-site cyclotron. We describe the advantages and limitations of ⁶⁸Ga-DOTA peptide PET/CT imaging for the assessment

of gastroenteropancreatic NET referring to the available literature as well as to our experience, and finally highlight potential future perspectives.

Keywords ⁶⁸Ga-DOTA-TOC · ⁶⁸Ga-DOTA-NOC · ⁶⁸Ga-DOTA-TATE · PET/CT · NET

Introduction

Neuroendocrine tumours (NET) have historically been considered as rare tumours [1, 2]; however, recent incidence estimates suggest that they are more common than might be expected. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database indicates an increase in the reported annual age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000) [3].

Originating from neuroendocrine cells deriving from the neural crest [4], NET may arise in diverse anatomic locations and may be associated with symptoms resulting from the secretion of hormones or vasoactive peptides into the bloodstream. Based on the presence of hormone-related syndromes, NET may be classified into functional (33–50% of patients) and non-functional forms. Being part of the amine precursor uptake and decarboxylation cell system, NET can produce a large variety of substances since they take up, accumulate and decarboxylate amine precursors such as dihydroxy-phenylalanine (DOPA) and hydroxyl-tryptophane. Another typical feature of neuroendocrine cells is the expression of several receptors in high quantities [4].

Although NET may arise virtually anywhere in the human body, the most common location of NET primary lesions is the gastroenteropancreatic (GEP) tract, followed by the lungs. Less frequent sites include the skin, the adrenal glands, the thyroid and the genital tract [5]. Traditionally,

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GEP NET were classified based on their origin in the foregut (pancreas, stomach, duodenum), midgut (ileum, appendix) or hindgut (colon, rectum). However, the European Neuroendocrine Tumour Society and the American Joint Committee on Cancer have proposed also using the TNM staging system for NET of the foregut, midgut and hindgut [6, 7]. The use Ki67 levels to define the histological grade of NET has been proposed: low grade (grade 1), Ki67 <2%; intermediate grade (grade 2), Ki67 3% to 20%; high grade (grade 3), Ki67 >20% [6, 7]. The International Association for the Study of Lung Cancer has also recently recommended the use of the TNM staging system for pulmonary NET [8].

The small size of NET, their variable anatomical location and the slow metabolic rate of well-differentiated forms, have limited their detection using different imaging procedures. Traditionally, NET diagnostic work-up included morphological imaging procedures such as computed tomography (CT), ultrasonography (US) and magnetic resonance imaging (MRI) combined with functional imaging, namely whole-body somatostatin receptor scintigraphy (SRS) [9, 10]. As described by Chiti et al. in this issue, the introduction of SRS represented a milestone in the NET diagnostic flow-chart. In a study analysing more than 1,000 patients, Krenning et al. observed a higher accuracy of SRS as compared to other morphological imaging modalities [11] for the detection of both primary NET and their metastatic lesions.

Despite the high accuracy of SRS for the detection of NET, the recent introduction of novel somatostatin analogues labelled with ^{68}Ga (^{68}Ga -DOTA peptides) has completely revolutionized the traditional diagnostic approach to NET in specialized centres in Europe. The use of ^{68}Ga -DOTA peptide PET/CT offers several advantages over SRS. From a technical point of view, the synthesis of ^{68}Ga -DOTA peptides is relatively easy and economical, and can also be performed in centres without an on-site cyclotron. PET/CT imaging is less time-consuming than SRS (2 hours, instead of the 4 plus 24 hours acquisition). The possibility to semiquantify the activity in a given region of interest is another potential advantage of PET scanning over SRS and the SUVmax has recently been reported to be a prognostic factor [12]. Moreover, among the other advantages is the higher spatial resolution of the PET tomograph as compared to the gamma camera, providing better visualization of small lesions (<10 mm).

The synthesis of specific PET tracers for NET imaging has been pursued mainly as a consequence of the marginal role of FDG for the visualization of well-differentiated NET [13] and because of the difficulties in the synthesis of other PET tracers for NET imaging (e.g. ^{18}F -DOPA).

^{68}Ga -DOTA peptides are a group of PET tracers that specifically bind to somatostatin receptors (SST) that are over-expressed on NET cells. SST are G-protein-coupled

receptors and are internalized after specific ligand binding [14], and six different types have been identified (SST1, 2A, 2B, 3, 4 and 5) in humans. Structurally ^{68}Ga -DOTA peptides are made of an active part directly binding to SST (TOC, NOC, TATE), a chelate (DOTA) and the beta-emitting isotope (^{68}Ga). The main difference among the various tracers (DOTA-TOC, DOTA-NOC, DOTA-TATE) is the variable affinity to SST subtypes [15]: while all can bind to SST2 and SST5, only DOTA-NOC also shows good affinity for SST3. However, there is currently no evidence of a clinical impact of these differences in receptor binding affinity, and therefore there is no indication suggesting the preferential use of one compound over the others. The labelling with ^{68}Ga also presents advantages over other employed isotopes as reported by Antunes et al. [15] and DeCristoforo in this issue.

From the time of their first use in humans, the use of ^{68}Ga -DOTA peptides has increased exponentially, and the number of papers describing their use in patients with NET has risen considerably in the past few years. At present, their use is limited to clinical trials in specialized centres.

^{68}Ga -DOTA peptide synthesis

From a technical point of view, the synthesis process is relatively easy: ^{68}Ga can be easily eluted from a commercially available $^{68}\text{Ge}/^{68}\text{Ga}$ generator without the need for an on-site cyclotron. The long half-life of the mother radionuclide ^{68}Ge (270.8 days) makes it possible to use the generator for approximately 9–12 months depending on requirements. ^{68}Ga (half-life 68 min) is a positron emitter with 89% positron emission and negligible gamma emission (1,077 keV) of 3.2% only. For labelling, the ^{68}Ga eluate is first concentrated and purified using a microchromatography method [16]. Radiolabelling yields of >95% can usually be achieved within 15 min.

PET/CT imaging protocol using ^{68}Ga -DOTA peptides

PET/CT image acquisition using ^{68}Ga -DOTA peptides has recently been standardized [17]. PET/CT image acquisition starts at 60 min after intravenous injection of approximately 100 MBq (75–250 MBq) of the chosen radiolabelled peptide (^{68}Ga -DOTA-TOC, ^{68}Ga -DOTA-NOC, ^{68}Ga -DOTA-TATE). The amount of injected radioactivity strictly depends on the daily production of the generator for each single elution (usually in the range 300–700 MBq), by the tomograph characteristics (the use of 3-D tomographs is recommended) and, of course, by the number of patients scanned per day. The discontinuation of somatostatin analogue treatment before the PET/CT scan is not mandatory

and no clear evidence supports the need for discontinuing their use before scanning.

Considering that SST are widely dispersed within the human body, different organs may be imaged using ^{68}Ga -DOTA peptides, including the liver, spleen, pituitary, thyroid, kidneys, adrenal glands, salivary glands, stomach wall and bowel. A potential pitfall in image interpretation is represented by the uptake of tracer in the pancreatic head. Tracer uptake in the exocrine pancreas (head) has been reported to be a relatively frequent finding (Gabriel et al. [18] with DOTA-TOC, 67.8%; Castellucci et al. [19] with DOTA-NOC, 31%) and is not necessarily associated with the presence of active disease. Its clinical significance, however, as well as the detailed mechanism of uptake in the pancreatic head, are still unclear. Among the causes of potential pitfalls in image interpretation, inflammation needs to be considered, since SST are expressed on activated lymphocytes, and therefore ^{68}Ga -DOTA peptides may be falsely positive in inflamed areas. Moreover, an accessory spleen or physiological activity at the adrenal level may be other causes of false-positive reports.

Clinical use of ^{68}Ga -DOTA peptides in GEP NET

As stated above, several papers report the higher diagnostic accuracy of ^{68}Ga -DOTA peptide PET/CT as compared to conventional imaging procedures, SRS and other metabolic PET tracers used for NET imaging (^{18}F -DOPA, ^{18}F -FDG). However, most studies have included both patients with GEP and patients with non-GEP tumours, reporting overall sensitivity values. Indications for performing ^{68}Ga -DOTA peptide studies in patients with GEP NET include: staging, restaging after surgery or therapy, identification of the site of the unknown primary tumour in patients with proven NET secondary lesions, and selection of patients eligible for therapy with either cold or hot (peptide receptor radionuclide therapy) somatostatin analogues.

The following discussion covers the most commonly employed DOTA peptides in clinical practice: ^{68}Ga -DOTA-TOC, ^{68}Ga -DOTA-NOC and ^{68}Ga -DOTA-TATE.

^{68}Ga -DOTA-TOC in GEP NET

The first ^{68}Ga -DOTA peptide to be used in patients with NET was ^{68}Ga -DOTA-TOC. Several studies showed a high tumour to non-tumour contrast and a higher sensitivity of ^{68}Ga -DOTA-TOC PET/CT as compared to SRS [20, 21]. Hofmann et al. described a population of eight patients with pathologically proven NET (six with a GEP NET primary), and observed overall sensitivity for tumour detection with DOTA-TOC of 100% as compared to 85% of SRS [20]. The study with the largest patient population (84 patients with

NET; 53 with a documented GEP primary) showed overall higher sensitivity (97%) for DOTA-TOC PET compared to CT (61%) and SRS (52%) for the detection of NET lesions, especially in patients with small tumours at the nodal or bone level [18]. The accuracy of ^{68}Ga -DOTA-TOC for the detection of bone lesions was further investigated in detail in a recent study that compared PET data with conventional imaging findings and bone scintigraphy. In 51 patients with well-differentiated NET (35 with a GEP primary), PET with ^{68}Ga -DOTA-TOC performed better than CT and bone scintigraphy for the early detection of secondary lesions in bones (sensitivity 97%, specificity 92%) [22].

^{68}Ga -DOTA-NOC in GEP NET

^{68}Ga -DOTA-NOC is also increasingly used in several centres in Europe and worldwide. DOTA-NOC shows good affinity not only for SST2 and SST5, but also (in contrast to DOTA-TOC) for SST3 [15]. Moreover, ^{68}Ga -DOTA-NOC has been reported to have a more favourable dosimetry [23]. Similar to ^{68}Ga -DOTA-TOC, ^{68}Ga -DOTA-NOC has also been reported to show higher accuracy for the detection of NET lesions than both conventional imaging and SRS. In particular, ^{68}Ga -DOTA-NOC shows good sensitivity for the visualization of small lesions, particularly at the nodal and bone levels [24], or in patients with an unusual anatomical location [25]. Fanti et al. reported that ^{68}Ga -DOTA-NOC can be used for the evaluation of NET with uncommon presentations including tumours of the uterus, prostate, ovary, kidney, breast and ear, and paraganglioma [25].

Since NET may often present as lesions with small dimensions and may arise virtually anywhere in the human body, the detection of the primary tumour site in patients with proven NET secondary lesions is challenging for the clinician. In fact morphological conventional imaging procedures and SRS often fail to identify the primary tumour site. In a population of 59 patients, ^{68}Ga -DOTA-NOC PET/CT was able to detect of the primary tumour in 35 patients with cancer of unknown primary (CUP; in 32 of the 35, the primary was a GEP tumour), with an overall detection rate of 59% [26].

Of course, the introduction of a more sensitive imaging procedure (such as PET/CT with ^{68}Ga -DOTA peptides), although very appealing for both researchers and clinicians, may not always have a direct impact on the clinical management of patients. In fact in most patients the detection of a higher number of metastatic lesions in comparison to morphological imaging or SRS is not followed by a change in the therapeutic approach. On the contrary, the detection of unsuspected metastatic spread or local relapse, the identification of the site of the occult primary tumour or the confirmation or exclusion of SSR expression on tumour cells are all conditions that can modify the therapeutic approach. The clinical impact of DOTA-NOC PET/CT was evaluated

in a population of 90 NET patients (62 with a GEP primary) [27], and overall the PET/CT findings affected either stage classification or therapy modifications in half the patients. It is interesting to note that as a consequence of being a receptor-based tracer, the most frequent clinical setting in which PET provided an impact on management was the therapeutic approach (initiation/continuation of hot or cold somatostatin analogues, in 36 of the 90 patients) followed by surgical indication/exclusion. Less frequent impacts on management included the initiation of radiotherapy, further diagnostic investigation and liver transplantation [25].

At present, ^{68}Ga -DOTA-NOC is the only tracer studied with the aim of defining PET/CT-derived parameters to predict patient outcome. In fact the observations that well-differentiated NET show a slower growth rate, higher SST expression, higher ^{68}Ga -DOTA-NOC uptake, higher response rate to somatostatin analogues and better outcome, have raised the issues of whether it is possible to define SUVmax values that may predict a more favourable outcome. In a population of 47 patients with NET (41 with a GEP primary), ^{68}Ga -DOTA-NOC PET/CT SUVmax values were found to provide prognostic information [12]: patients with stable disease or partial response showed significantly higher SUVmax than those with progressive disease. In particular, the best SUVmax cut-off to differentiate between these two groups of patients was reported to range between 17.6 and 19.3 (SUVmax values higher than 19.3 permitted the selection of patients with slower disease progression). Interestingly the authors also reported higher SUVmax values in patients with a pancreatic primary as compared to those with other primary locations.

^{68}Ga -DOTA-TATE in GEP NET

Compared to other ^{68}Ga -DOTA peptides, ^{68}Ga -DOTA-TATE shows an extremely selective affinity for SST2 [15, 28], the most common SST subtype on NET cells. Similar to ^{68}Ga -DOTA-TOC and ^{68}Ga -DOTA-NOC, ^{68}Ga -DOTA-TATE has also been reported to be superior to SRS for NET lesion detection. In a population of 51 NET patients (37 with a GEP primary) with either negative (35) or equivocal (16) SRS, ^{68}Ga -DOTA-TATE PET/CT identified significantly more lesions than SRS with a change in management in 36 patients [29].

Comparative studies: ^{68}Ga -DOTA peptides vs. other PET tracers for NET detection

Considering the complex biology of NET cells, several compounds have been proposed for the imaging of NET. The most commonly used metabolic tracer to study well-differentiated NET is ^{18}F -DOPA. To our knowledge there is only one

Table 1 NET identification by ^{68}Ga -DOTA-NOC PET/CT in 1,239 patients with proven or suspected NET

	No. (%) of patients
Primary tumour site, GEP NET	
Appendix	28 (2.3)
Colon	11 (0.9)
Gallbladder	2 (0.2)
Gastric	21 (1.7)
Duodenum	21 (1.7)
Ileum	258 (20.8)
Ileum + pancreas	1 (0.1)
Jejunum	4 (0.3)
Pancreas	314 ()
Pancreas (insulinoma)	2 (0.2)
Pancreas + duodenum	8 (0.6)
Total	670 (54.1)
Primary tumour site, non-GEP NET	
Breast (papillary adenocarcinoma with neuroendocrine component)	6 (0.5)
Chondrosarcoma with neuroendocrine component	2 (0.2)
Ear	10 (0.8)
Pituitary	3 (0.2)
Idiopathic diffuse pulmonary neuroendocrine cell hyperplasia	1 (0.1)
Kidney	5 (0.4)
Larynx	2 (0.2)
Lung	154 (12.4)
Lung (microcytoma)	4 (0.3)
Melanoma	1 (0.1)
Meningioma	4 (0.3)
Merkel cell	9 (0.7)
Neurofibrosarcoma	1 (0.1)
Ovary	3 (0.2)
Paraganglioma	24 (1.9)
Parathyroid	2 (0.2)
Phaeochromocytoma	15 (1.2)
Prostate	3 (0.2)
Rectum	5 (0.4)
Testicles	4 (0.3)
Thymus	4 (0.3)
Thyroid (medullary)	46 ()
Uterus	3 (0.2)
Total	311 (25.1)
Genetic syndromes	
Multiple endocrine neoplasia	62 (5.0)
von Hippel-Lindau	3 (0.2)
Total	65 (5.2)
Cancer of unknown primary	81 (6.5)
NET not confirmed	112 (9.0)
Total	1,239 (100.0)

Table 2 ^{68}Ga -DOTA-NOC PET/CT results in 1,239 patients with proven or suspected NET

Indication	No. (%) of patients	True-positive	True-negative	False-positive	False-negative	Sensitivity (%)	Specificity (%)
Staging	94 (7.6)	81	1	0	12	87.1	100.0
Restaging	464 (37.4)	339	115	3	7	98.0	97.5
Equivocal conventional imaging	136 (11.0)	55	67	4	10	84.6	94.4
Equivocal SRS	7 (0.6)	1	6	0	0	na ^a	na ^a
Follow-up	281 (22.7)	72	207	2	0	100.0	99.0
Screening MEN	4 (0.3)	0	4	0	0	na ^a	na ^a
CUP	105 (8.5)	81 ^b	0	0	24	77.1 ^b	na
Suspected relapse (increased markers)	22 (1.8)	6	16	0	0	100.0	100.0
Suspected NET	126 (10.2)	17	108	0	1	94.4 ^c	100 ^c
Total	1,239 (100.0)	652	524	9	54	92.4	98.3

na not applicable.

^a Not applicable because of small patient subgroup.

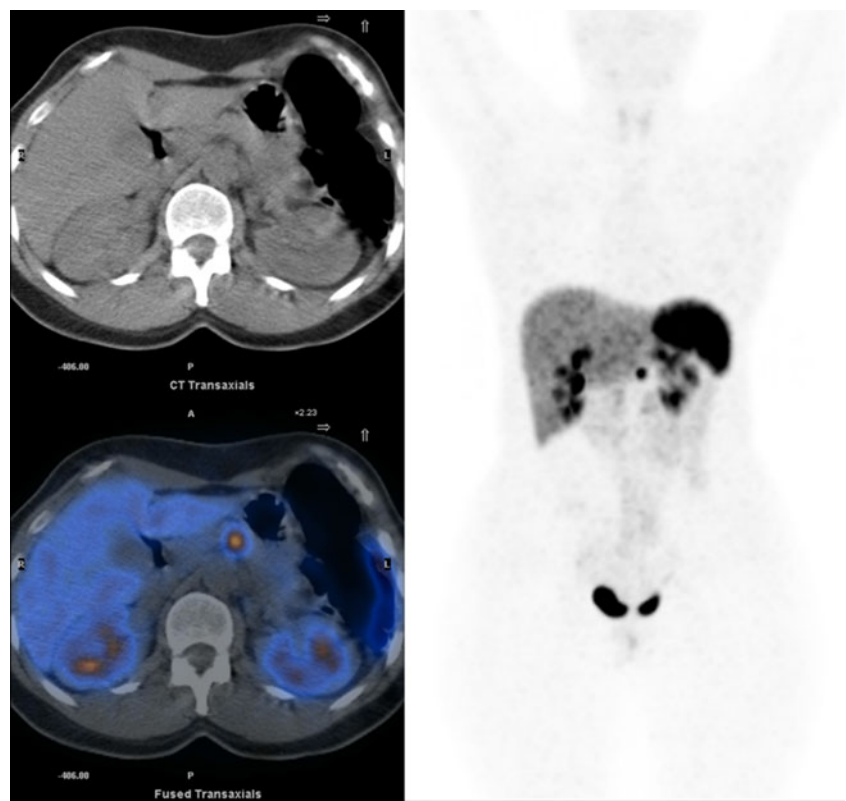
^b PET considered positive when at least one lesion was detected.

^c A true-positive finding in only 17 out of 126 patients should be born in mind when considering this result (see text).

study involving a direct comparison between ^{68}Ga -DOTA-NOC and ^{18}F -DOPA. In a limited patient population (13 patients, 11 with a GEP primary) a higher detection rate was found for ^{68}Ga -DOTA-NOC [30]. Similarly, in a population of 25 patients (14 with a GEP primary), ^{68}Ga -DOTA-TATE showed 54 out of 55 NET lesions in contrast to 29 lesions with ^{18}F -DOPA (sensitivity 96% vs. 56%) [31].

^{18}F -FDG may also play a role in the detection of NET lesions. Although the role of FDG is limited by the slow metabolic rate of NET cells, it should be remembered that NET may show variable degrees of differentiation between patients, in different lesions in the same patient and within different areas of the same tumour [32]. The detection of FDG uptake in lesions is clinically relevant since it depicts

Fig. 1 ^{68}Ga -DOTA-NOC PET/CT staging images in a patient with pancreatic NET. A focal area of pathological tracer uptake is present in the pancreatic body (SUVmax 27), and the presence of secondary lesions is excluded



the presence of less-differentiated tumour cells that are associated with a worse prognosis and require a different therapeutic approach, including systemic chemotherapy. A few studies have compared the differential uptake patterns of DOTA peptides (DOTA-TOC and DOTA-TATE) and FDG in non-GEP NET (lung NET and medullary thyroid carcinoma). Although the detailed analysis of non-GEP NET is beyond the scope of this review, it is relevant to observe that in non-GEP NET high uptake of ^{68}Ga -DOTA peptides is seen in low-grade NET, while FDG uptake is seen in high-grade tumours [33, 34]. From a clinical point of view, ^{18}F -FDG may be considered superior to ^{68}Ga -DOTA peptides in patients with low-differentiated NET (low SST expression) or in forms of NET characterized by a low expression of SST (e.g. medullary thyroid carcinoma).

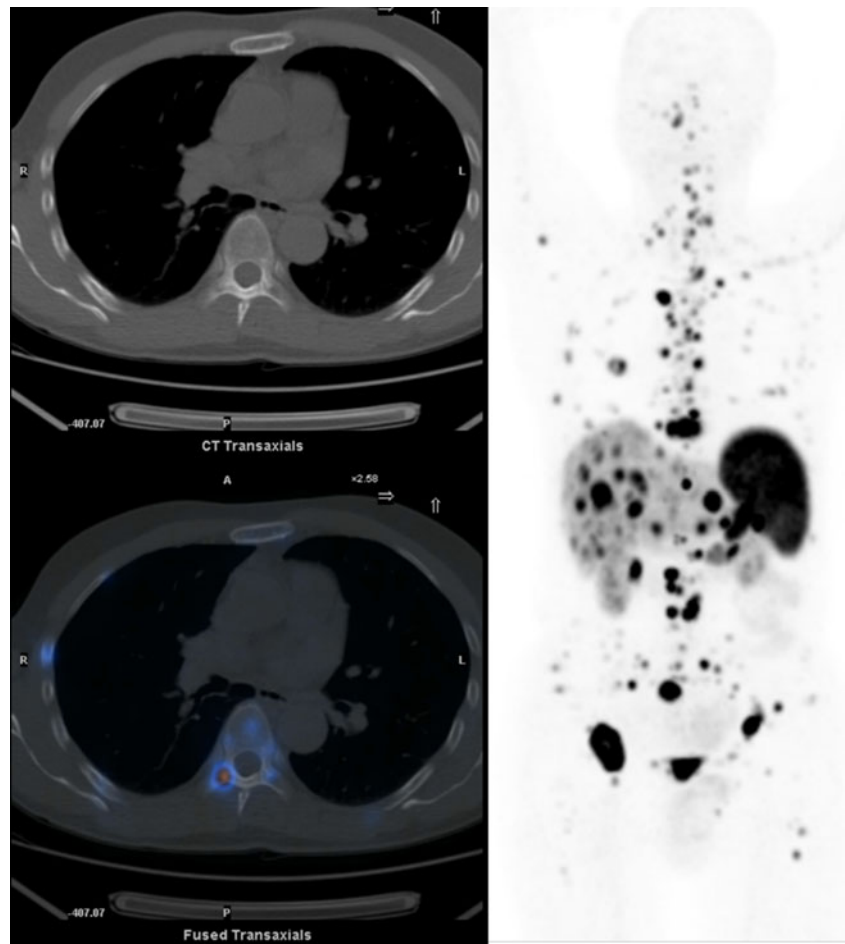
Our experience in more than 1,000 patients with NET studied by ^{68}Ga -DOTA-NOC PET/CT

Krenning et al. [11] reported their experience on the use of SRS in more than 1,000 patients with NET, stating the many advantages of using SRS over CT. Although the introduc-

tion of PET/CT with ^{68}Ga -DOTA peptides certainly represents a major advance in the diagnostic approach to patients with NET, offering higher accuracy for NET lesion detection and technical advantages, the role of SRS still needs to be underlined. Currently there is no evidence supporting the clinical advantages of performing PET/CT with ^{68}Ga -DOTA peptides in patients with NET and an existing pathological SRS-documented metastatic disease. The presence of equivocal or negative SRS raises the issue as to whether it is appropriate to perform PET/CT with ^{68}Ga -DOTA peptides in order to exclude (or confirm) the presence of lesions under 10 mm or to better investigate areas where octreotide physiologically shows a higher uptake (e.g. liver and bowel). It is easier to draw conclusions as to whether a technique is appropriate or not when dealing with a large patient population. Therefore, similar to the Rotterdam group, we decided to include a brief summary of the results we obtained using ^{68}Ga -DOTA-NOC PET/CT at our centre in order to provide data on a large population of patients with NET.

In February 2007, we introduced ^{68}Ga -DOTA-NOC PET/CT scanning as part of the diagnostic work-up of NET patients. All patients with NET were included in a

Fig. 2 ^{68}Ga -DOTA-NOC PET/CT staging images in a patient with pancreatic NET. Primary tumour in the pancreatic tail (SUVmax 36) is confirmed and multiple secondary lesions at the liver, node and bone levels are shown



study protocol to assess the accuracy of ^{68}Ga -DOTA-NOC PET/CT for NET lesion detection. In particular, in all patients, data regarding the pathological confirmation of NET, conventional imaging studies (performed within a month of the PET/CT scan), laboratory data and clinical follow-up were recorded. In consideration of the very good results obtained in terms of diagnostic accuracy, economic burden and patient compliance, our Institution decided to discontinue SRS at the end of 2007 in favour of ^{68}Ga -DOTA-NOC PET/CT. The study protocol for ^{68}Ga -DOTA-NOC PET/CT in NET patients was approved by the local ethics committee. At the time of this report the study was on-going, and therefore still collecting data regarding both new patients with NET and clinical and imaging follow-up information following older studies.

Overall, we have studied 1,239 patients with either pathologically proven or suspected NET by ^{68}Ga -DOTA-NOC PET/CT. Pathological confirmation was obtained by either surgical (819 of the 1,239 patients) or biopsy specimens (308 of 1239) while in 112 patients no tumour could be identified (108 suspected NET, 4 equivocal SRS). In the majority of patients (Table 1), the primary tumour arose from the GEP tract (670 patients, 54.1%) while among the patients with non-GEP NET (311, 25.1%), the lung was the most frequent primary site (158, 12.8%). Genetic syndromes accounted for the tumour in only a minority of the studied patients, including 62 with multiple endocrine neoplasia

Fig. 3 ^{68}Ga -DOTA-NOC PET/CT images in a patient with multiple secondary NET lesions in the liver studied to identify the unknown primary site. A focal area of tracer uptake in the duodenum (SUVmax 17) is compatible with the primary tumour site. Multiple areas of uptake at the liver and nodal (paracaval) levels are also shown. Surgical excision of the identified primary lesion provided confirmation of the PET findings

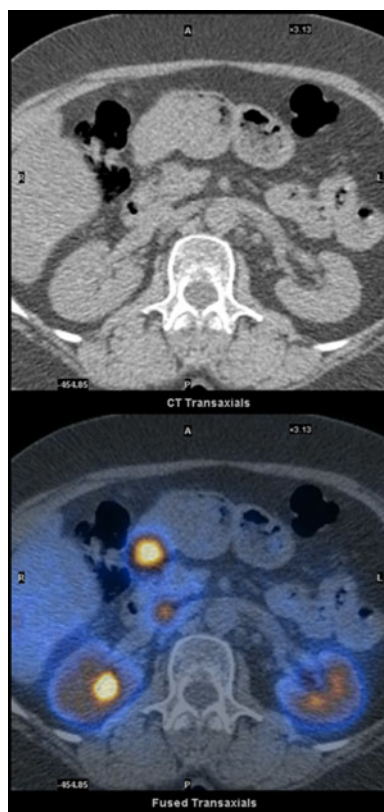


Table 3 Overall ^{68}Ga -DOTA-NOC PET/CT results in 1,239 patients with proven or suspected NET

PET finding	No. (%) of patients	True-positive	True-negative	False-positive	False-negative
Negative	576 (46.5)	0	522	0	54
Positive	655 (52.9)	647	0	8	0
Equivocal	8 (0.6)	5	2	1	0
Total	1,239 (100.0)	652	524	9	54

(MEN) and 3 with von Hippel-Lindau syndrome, while in 81 patients with CUP (6.5%) the site of the primary tumour could not be identified. Finally, in the remaining 112 patients studied for suspicion of NET, the presence of tumour was not confirmed either by PET or on follow-up.

Indications for performing PET/CT (Table 2) included staging (Figs. 1 and 2), restaging (after surgery or therapy), identification of the site of the primary tumour, screening in MEN, equivocal conventional imaging, equivocal SRS, follow-up, suspected relapse or suspected NET.

Considering all patients (Table 3), PET was positive in 655, negative in 576 and equivocal in 8. Comparing the results with conventional imaging and follow-up data, ^{68}Ga -DOTA-NOC PET/CT was true-positive in 652, true-negative in 524, false-positive in 9 and false-negative in 54 patients. Overall (Table 2), ^{68}Ga -DOTA-NOC PET/CT

showed good sensitivity (92%) and specificity (98%) for the detection of NET. The mean SUV_{max} of positive lesions was 22.8 ± 18.6 [2.2–150.0].

The most frequent cause of the false-positive PET findings (9 patients) was the presence of inflammation due to the expression of SST on activated lymphocytes. The causes of the false-negative PET findings (54 patients) included lesion size under 5 mm (14 patients; 7 gastric, 3 lung, 1 idiopathic diffuse neuroendocrine cell hyperplasia, 1 liver, 1 Merkel cell, 1 pancreas), lesions at sites of physiological ⁶⁸Ga-DOTA-NOC uptake (6 pancreatic head, 1 pituitary), factors related to tumour biological characteristics that would account for low/variable SST expression (1 insulinoma, 1 pheochromocytoma, and 10 moderate to low differentiation NET, including small cell lung cancer). In the remaining 21 patients studied for CUP, PET was negative and the site of the primary could not be identified. We frequently observed focal ⁶⁸Ga-DOTA-NOC uptake at the head of the pancreas (56 patients, 4.5%) not related to the presence of tumour.

In our series, ⁶⁸Ga-DOTA-NOC PET/CT was useful for the detection of the site of the primary tumour in patients with documented secondary NET lesions (Fig. 3). Among 105 patients studied for CUP, PET/CT allowed the detection of the primary tumour site in 24 (22.8%), confirmed the presence of secondary lesions in 60 but did not show the primary site, and was false-negative in 21.

Among the patients studied for suspected NET or suspected relapse, when the suspicion arose from the detection of increased levels of biochemical markers alone (66 and 22 patients, respectively), the majority of patients were true-negative (64 of 66 and 16 of 22, respectively). A high rate of true-negative results was also seen in patients presenting with chronic diarrhoea alone (4 of 5).

Conclusions and future perspectives on ⁶⁸Ga-DOTA peptides PET/CT

⁶⁸Ga-DOTA peptides PET/CT is increasingly used for the assessment of patients with well-differentiated NET in specialized centres in Europe. Several studies have shown the higher accuracy of ⁶⁸Ga-DOTA peptides for the detection of NET lesions as compared to both conventional imaging and SRS. The advantages of the use of ⁶⁸Ga-DOTA peptides are not merely limited to a better overall accuracy but also to the fact that they provide valuable data regarding the pattern of expression of SST on target lesions, which represents a useful non-invasive modality to select patients for therapy with either hot or cold somatostatin analogues. From a technical point of view it is also worth mentioning the relatively easy and economical synthetic process of these compounds that renders them suitable for use even in small centres without an on-site cyclotron.

The potential association of ⁶⁸Ga-DOTA peptide PET/CT with PET/CT using metabolic tracers may prove valuable in patients presenting with intermediate- to high-grade tumours (¹⁸F-FDG) or for assessing response to therapy (¹⁸F-DOPA). However, further data are needed to further elucidate the role of the integrated use of metabolic and receptor-targeted tracers in the clinical management of patients with NET.

Considering the expression of a wide range of receptors on the surface of NET cells, further studies are needed to ascertain whether the use of alternative radiolabelled ligands, currently used only in the preclinical setting, may provide additional value in the management of patients with NET.

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

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