Original article

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The role of ^{68}Ga-DOTA-NOC PET/CT in evaluating neuroendocrine tumors: real-world experience from two large neuroendocrine tumor centers

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Objective Our aim was to assess the role of ^{68}Ga-DOTA-NOC PET/CT as a tool for the management of neuroendocrine tumors (NETs), evaluating the clinical impact on patients from two large NET centers in different geopolitical settings.

Patients and methods This is a retrospective study of patients with NETs who underwent ^{68}Ga-DOTA-NOC PET/CT at Royal Liverpool University Hospital (UK) and at Mount Lebanon Hospital (Lebanon). Indications for imaging and findings of the PET/CT along with demographic and clinical outcome data were recorded and evaluated.

Results Four hundred and forty-five patients fulfilled the inclusion criteria, with a median age at the time of diagnosis of 56 (range: 3–90) years; 248 (55.7%) patients were male. ^{68}Ga-DOTA-NOC PET/CT was indicated for staging in 193 (43.4%) patients, for diagnosis in 124 (27.9%) patients, for follow-up in 97 (21.7%) patients, and for identification of a primary NET site in 31 (7%) patients. One hundred and four (27.9%) patients underwent ^{68}Ga-DOTA-NOC PET/CT for the primary diagnosis of NET, of whom 66 (52.7%) patients presented with a clinical suspicion of NET, 10 (8.3%) patients presented with a biochemical suspicion of NET only, and 48 (38.8%) patients presented with a suspicious NET lesion discovered on another imaging modality. The most common clinical presentation was typical carcinoid syndrome [4 (33%) patients]. Results on the basis of histology were used as the gold standard for the diagnosis in 57% of patients and the remaining on the basis of follow-up as per established clinical consensus. Sensitivity, specificity, negative-predictive value, and positive-predictive value of PET/CT were 87.1, 97.7, 79.6, and 98.7%, respectively, for the entire sample. Accuracy was measured using the receiver operating characteristic curve analysis with an area under the curve of 0.924 (95% confidence interval: 0.874–0.974).

Conclusion ^{68}Ga-DOTA-NOC PET/CT is a highly sensitive and specific study for the diagnosis and follow-up of patients with neuroendocrine tumors. These results support the use of ^{68}Ga-DOTA-NOC PET/CT contributing significantly toward the clinical management of NET patients. *Nucl Med Commun* 38:170–177 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Neuroendocrine tumors (NETs) form a heterogeneous group of tumors that share a common embryological origin from the ectodermal neural crest and the ability to produce amines and hormones from precursors [1]. These tumors include adenomas from the pituitary gland, islet cell tumors from the pancreas, pheochromocytoma and neuroblastoma from the adrenal medulla, medullary thyroid carcinoma from the C-cells of the thyroid gland, carcinoid tumors from the gastrointestinal tract (or less often from the lung), and paragangliomas [2]. The wide spread of neuroendocrine cells throughout the body and the vast array of hormones that they produce make the diagnosis of NETs a diagnostic challenge for physicians. To make the task even more difficult, these tumors are usually small at presentation and conventional anatomical imaging usually fails to locate them.

Functional imaging with somatostatin analogues has been used for the early detection of these tumors, pretherapy staging, tumor recurrence, and response assessment to treatment [2]. Although lacking an anatomical definition, these techniques have the advantages of detecting early malignant changes before anatomical disruption is evident, and whole-body scanning to exclude distant metastasis [3].

Gallium-68 (^{68}Ga)-labeled-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-peptides are new

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somatostatin-analogue PET molecules that have been developed over the past 5 years. These molecules showed promising results for the early diagnosis of NETs and detection of tumor implants with high sensitivity and specificity. The advent of these molecules will improve the diagnostic imaging capabilities and management of NETs [4].

This study aimed to assess the role of ^{68}Ga-DOTA-NOC PET-CT in a large population of NET patients from two tertiary NET centers, as a tool for management of NETs, evaluating the clinical impact on patients from two large NET centers in different geopolitical settings.

Patients and methods

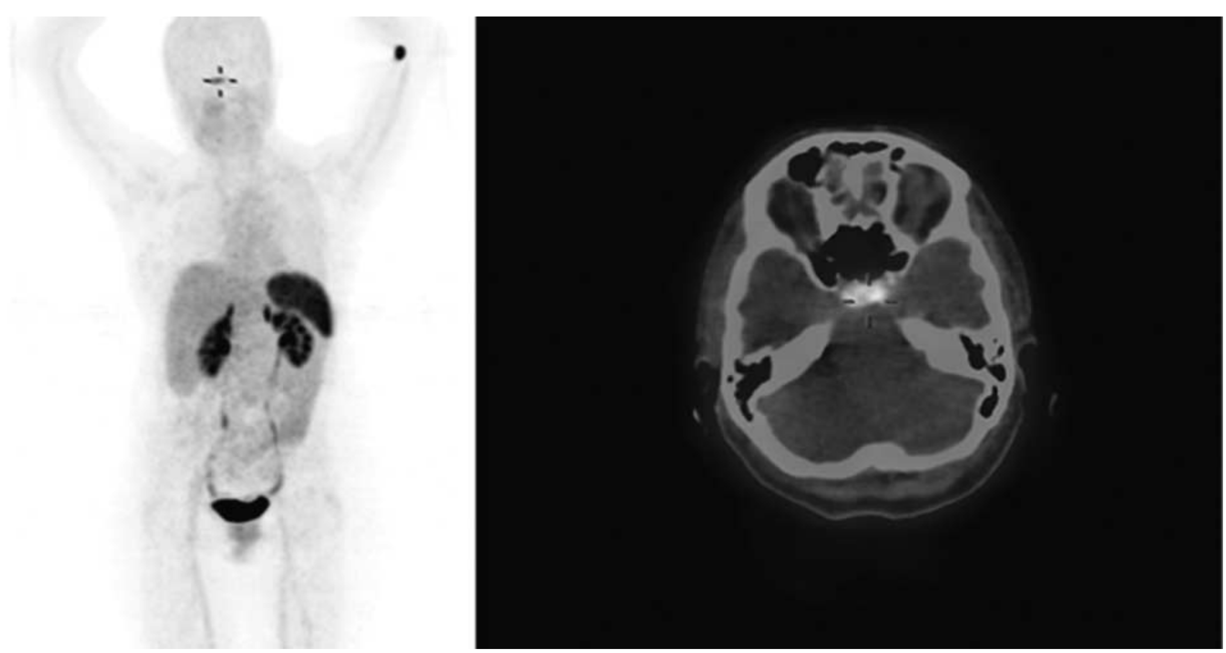
This was a retrospective study carried out between May 2010 and January 2015 at Mount Lebanon Hospital, Beirut, Lebanon, and between May 2013 and August 2015 at Royal Liverpool University Hospital, Liverpool, UK, after obtaining the approval of Institutional Review Boards.

All patients underwent a PET/CT scan 1 h after an intravenous injection of ^{68}Ga-DOTA-NOC (dosage ranged between 120 and 180 MBq produced from an ITG gallium generator; ITG, Garching, Germany) for staging, recurrence, follow-up, or search for primary NET site.

Statistical analysis was carried out using IBM USA SPSS, version 22.0 (IBM, Armonk, New York, USA). Variables included in the analysis were as follows: age at diagnosis, sex, and indication for PET (detection, staging, follow-up, and search for a primary). Sensitivity and specificity analyses were carried out after considering as gold standard the final histopathological result or the final diagnosis after follow-up. NET lesions were confirmed on follow-up exams by their progression pattern compared with the baseline examinations. In 43% of patients who did not have a histopathological confirmation of NET, a minimum of two (mean of 2.3) follow-up scans with distinct behavioral patterns of a NET tumor, along with correlative clinical, biochemical, and cross-sectional imaging behavior, were considered before we labeled the patients as having a NET tumor. The accuracy of PET was evaluated by means of a receiver operating characteristic curve analysis. The test was considered very accurate if the area under the curve was more than 0.8.

PET/CT at both centers was performed according to standardized protocols. Image acquisition was started 1 h after injection. Whole-body computed tomography (CT) without contrast was performed first on the basis of a topogram. It was immediately followed by the acquisition of six or seven PET increments in steps of 3 min per increment. Images obtained with these two modalities were then fused to locate specific high-grade avid lesions. To improve the sensitivity of PET/CT when we had mismatched fused images related to patients' movements, some patients benefited from a supplementary late acquisition at 2 h centered on specific regions.

Fig. 1



Normal whole-body PET/CT with ^{68}Ga-DOTA-NOC showing the physiological distribution of the tracer homogenously within the pituitary gland, spleen, urinary system, liver, and bowels. CT, computed tomography.

Figure 1 shows the physiological distribution of ^{68}Ga-DOTA-NOC in the whole body.

Results

Four hundred and forty-five patients fulfilled the inclusion criteria, among whom 248 (55.7%) were male and the median age at diagnosis was 56 (range: 3–90) years. In all, 316 cases were from the Royal Liverpool University Hospital (UK) and 129 cases were from Mount Lebanon Hospital (Lebanon).

^{68}Ga-DOTA-NOC PET/CT was indicated mainly for staging in 193 (43.4%) patients, for diagnosis in 124 (27.9%) patients, for follow-up in 97 (21.7%) patients, and finally for search for a primary NET site in 31 (7%) patients.

One hundred and four (27.9%) patients had ^{68}Ga-DOTA-NOC PET/CT for the primary diagnosis of NET, of whom 66 (52.7%) patients presented with a clinical suspicion of NET, 10 (8.3%) patients presented with a biochemical suspicion of NET only, and 48 (38.8%) patients presented with a suspicious NET lesion discovered on another imaging modality. The most common clinical indication was typical carcinoid syndrome ($n = 41$).

Table 1 summarizes the clinical information and pathologic results for all patients. Figure 2 summarizes the sites of primary NET in 312 patients.

Results on the basis of histology were used as the gold standard for diagnosis in 252 (56.6%) patients and the remaining on the basis of follow-up. Sensitivity, specificity, negative-predictive value, and positive-predictive value of PET/CT were 87.1, 97.7, 79.6, and 98.7%, respectively, for the entire sample. Accuracy was measured using the receiver operating characteristic curve analysis with an area under the curve of 0.924 (95% confidence interval: 0.874–0.974). Table 2 shows the results of analysis for each indication of PET/CT (Figs 3 and 4).

Table 1 Demographic and pathology results

	n (%)
Sex	
Female	248 (44.3)
Male	197 (55.7)
Age (years)	
Mean	54
Median	56
Maximum	90
Minimum	3
SD	17.1
Indication for PET/CT	
Diagnosis	124 (27.9)
Staging	193 (21.7)
Follow-up	97 (7.0)
Search for primary	31 (43.4)
Types of indication	
Clinical suspicion	66 (52.8)
Radiological evidence	48 (38.9)
Biochemical	10 (8.3)
Indication for diagnosis	
Chronic diarrhea	4 (3.23)
Increased chromogranine A	4 (3.23)
Increased urinary catecholamine	4 (3.23)
Ascites	5 (4.03)
Hyperinsulinemia	3 (2.42)
Hypertension	11 (8.87)
Bone lesion	3 (2.42)
Adrenal mass	4 (3.23)
Appendiceal mass	3 (2.42)
Cervical mass	4 (3.23)
Gastric mass	6 (4.84)
Hepatic lesion	3 (2.42)
Lung lesion	5 (4.03)
Pancreatic mass	10 (8.06)
Retroperitoneal mass	10 (8.06)
Ulcers	4 (3.23)
Typical carcinoid syndrome	41 (33.06)
Pathology of NET	
Ampulla of vater	3 (1.0)
Anal	3 (1.0)
Appendiceal	12 (3.9)
Bladder	3 (1.0)
Small bowel	42 (13.8)
Bronchial	3 (1.0)
Cecal	3 (1.0)
Large bowel	6 (1.9)
Duodenal	6 (1.9)
Gastric	28 (8.7)
Insulinoma	3 (1.0)
Mediastinal	9 (2.9)
Medullary thyroid carcinoma	27 (7.8)
MEN syndrome	3 (1.0)
Metastatic NET, unknown primary	36 (11.7)
Nasopharynx	3 (1.0)
Neuroblastoma	12 (3.9)
Ovarian NET	3 (1.0)
Paraganglioma	3 (1.0)
Pheochromocytoma	6 (1.9)
Pancreatic	84 (27.2)
Rectal	9 (2.9)
Retroperitoneal	6 (1.9)
Sigmoid	3 (1.0)
Type of gold standard	
Follow-up	193 (43.4)
Histology	252 (56.6)

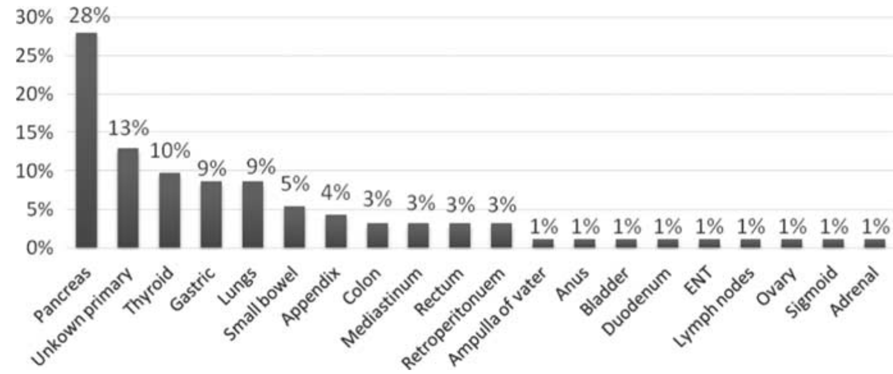
CT, computed tomography; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumor.

Discussion

The major role of imaging in NETs is localizing and staging the primary lesion, especially in the case of functioning tumors that are usually small and pose a diagnostic challenge. Preoperative localization reduces the potential surgical complications and increases the chances of surgical resection, the only form of curative treatment for these tumors.

CT scans are used in the primary diagnosis of NET in patients with clinical or biochemical evidence. They are also essential in evaluating the local spread of a NET and its distant metastasis, especially hepatic. NETs are characterized by their highly vascular nature, enhancing early in the arterial phase (20 s) of iodinated contrast CT, with washout during the portal phase (70 s) [5]. The specificity and sensitivity of CT scans depends on the tumor size and localization, for example multiphasic CT scans have sensitivity up to 80% in detecting primary pancreatic NETs. This sensitivity is highly influenced by

Fig. 2



The sites of primary neuroendocrine tumor.

Table 2 Analysis of ^{68}Ga-DOTA-NOC PET/CT

Reasons for PET/CT	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy AUC
Diagnosis	90	96.2	96.2	90	0.931
Follow-up	90.5	100	77.8	100	0.952
Search for primary	88.9	NA	NA	100	NA
Staging	84.4	100	61.1	100	0.922

AUC, area under the curve (receiver operating characteristic curve analysis); > 0.8 considered very accurate; CT, computed tomography; NA, not applicable; NPV, negative-predictive value; PPV, positive-predictive value.

tumor size, with no tumors identified under 1 cm, 30% of tumors between 1 and 3 cm detected, and almost all large (>3 cm) nonfunctioning tumors demonstrated (95–100%) [6]. Detection is also influenced by the site of tumor; one prospective study detected 68% of primary tumors and 86% of hepatic metastases; 90% were pancreatic head tumors, 80% were pancreatic body tumors, and 45% were pancreatic tail tumors [7].

MRI now has a sensitivity that equals or exceeds CT in localizing primary pancreatic tumors. For hepatic metastasis detection, MRI is widely considered to be the most sensitive modality. Sensitivity as high as 94% was reported for pancreatic masses detection, but as with CT, this sensitivity varies with tumor size [8].

PET/CT studies reflect the different functional and metabolic pathways of NETs, such as glucose metabolism [fluorine-18-fluorodeoxyglucose (^{18}F-FDG)], the uptake of hormone precursors (^{11}C-5-hydroxytryptophan; ^{11}C-dihydroxyphenylalanine or ^{18}F-dihydroxyphenylalanine; ^{18}F-fluorodopamine), the expression of receptors (^{68}Ga-labeled somatostatin analogues), as well as the synthesis, storage, and release of hormones (^{11}C-hydroxyephedrine and others) [9].

Rapidly growing tumors have accelerated glucose metabolism and will concentrate ^{18}F-FDG much more than normal cells, enabling their visualization [10]. However, most NETs are well differentiated, slowly growing tumors and have a lower metabolic profile, hence the low sensitivity of ^{18}F-FDG PET/CT in their detection [11]. ^{18}F-FDG PET/CT is only used in the diagnosis of rapidly growing, poorly differentiated NETs; ^{18}F-FDG PET/CT sensitivity for benign pheochromocytoma, for example, is 58%, whereas it is as high as 88% for malignant pheochromocytoma and is the procedure of choice [12]. ^{18}F-FDG PET/CT also has a high sensitivity of 96% in detecting medullary thyroid carcinoma [13].

^{68}Ga is a positron emitter with a half-life of 68 min that is used currently for labeling somatostatin analogues for PET/CT imaging of NETs. The synthetic somatostatin analogues such as tetra-azacyclododecanetetraacetic acid-D-Phe(1)-Tyr(3)-octreotide (DOTA-TOC) can be readily labeled with ^{68}Ga. ^{68}Ga-labeled peptides have a high affinity for SSTR-2, SSTR-3, SSTR-5 and intermediate affinity for SSTR-4, and are rapidly accumulated in NETs.

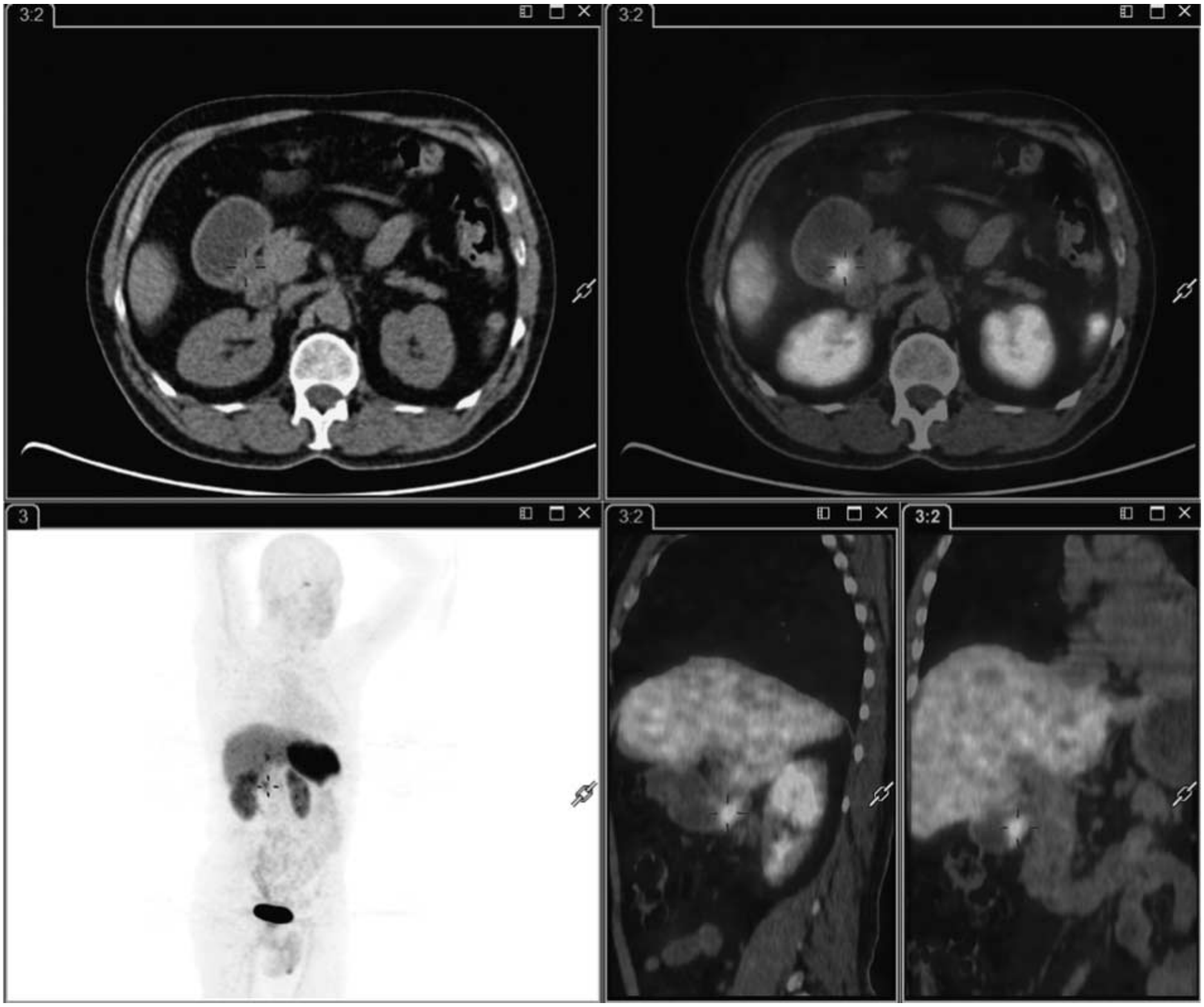
The preclinical and clinical applications of this technique have been successful in a variety of tumors, particularly NETs, with a significant impact on patient management and outcome [14].

A small study carried out by Gabriel *et al.* [15] compared ^{68}Ga-DOTA-TOC PET/CT using conventional scintigraphy with ^{99m}Tc-HYNIC-TOC and ^{111}In-DOTA-TOC.

Frilling and colleagues have reported the superiority of ^{68}Ga-DOTA-TOC PET/CT over conventional imaging (CT/MRI) in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). On the basis of a series of 52 patients, PET/CT altered the treatment plan in 31 (59.6%) patients [16].

In a recent meta-analysis by Yang and colleagues using 10 studies comprising 416 patients with NETs, the pooled sensitivity of ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-D-Phe1-Tyr3-octreotat (DOTA-TATE) PET/CT in the

Fig. 3



A 59-year-old man referred for staging of a neuroendocrine tumor at the level of the duodenum diagnosed recently after gastroduodenoscopy. ^{68}Ga-DOTA-NOC PET/CT shows an active lesion within the duodenum corresponding to subcentimetric thickening on CT scan related to a primary neuroendocrine tumor. No active locoregional or distant metastasis was found on this exam. CT, computed tomography.

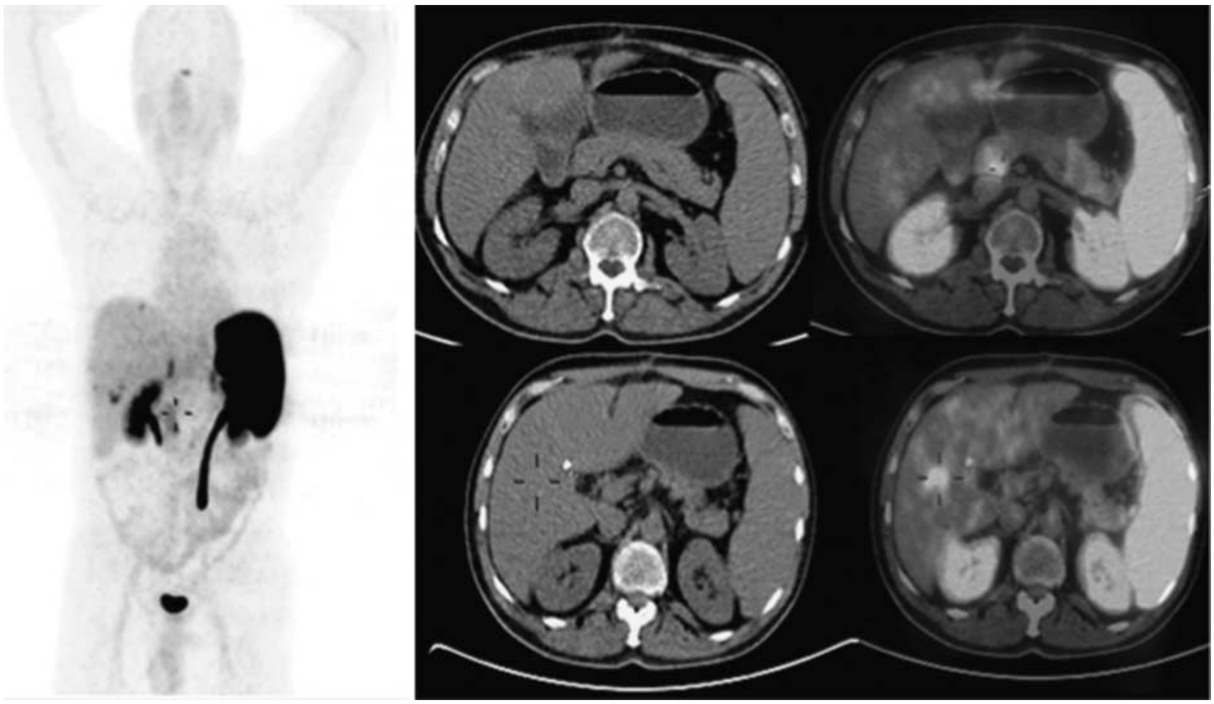
diagnosis of NETs calculated on a per-patient-based analysis was 93% (95% confidence interval: 89–96%) and 96%. The pooled specificity of ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-TATE PET/CT in diagnosing NETs was 85 and 100%, respectively [17].

In a more recent prospective study, Sadowski *et al.* [18] showed that ^{68}Ga-DOTA-TATE PET/CT had a detection rate of 95.2% compared with detection rates of 45.6 and 30.9% for anatomic and ^{111}In-pentetreotide SPECT/CT imaging, respectively, and concluded that ^{68}Ga-DOTA-TATE PET/CT imaging is more sensitive for staging and detecting unknown primary GEP-NETs than is ^{111}In-pentetreotide SPECT/CT and anatomic imaging with CT and MRI.

Haug and colleagues reported the role of ^{68}Ga-DOTA-TATE PET/CT in suspected NETs. ^{68}Ga-DOTA-TATE PET/CT identified NET in 29 of the 36 cases and excluded the presence of a NET in 61 of the 68 non-NET patients, indicating a sensitivity of 81% and a specificity of 90% [19]. The PET/CT yielded a false-positive result in seven patients and a false-negative result in another seven patients, indicating positive and negative-predictive values of 81 and 90%, respectively, and an accuracy of 87%. They concluded that in patients with suspected NETs because of clinical symptoms, elevated levels of tumor markers, or indeterminate tumors suggestive of NET, ^{68}Ga-DOTA-TATE PET/CT is highly accurate, thus supporting its use in clinical routine diagnostics.

Treglia and colleagues evaluated 16 studies comprising 567 patients with GEP and thoracic NETs. The pooled sensitivity and specificity of ^{68}Ga-DOTA peptide PET/CT

Fig. 4



A 41-year-old man referred for staging of a suspected pancreatic mass. ^{68}Ga-DOTA-NOC PET/CT shows very active pancreatic lesion measuring 1.2 cm compatible with the primary pancreatic tumor. Small lesions are visualized within segment V of the liver in favor of liver metastasis, along with the dome of the liver. There was no evidence of extraintestinal localization notably within the lungs and bone. A mild physiological uptake was noted in the uncinate process without abnormality on the CT scan. CT, computed tomography.

or PET/CT in detecting NETs were 93 and 91%, respectively. They recommended the use of this technique as a first-line diagnostic imaging method in patients with suspicious thoracic and/or GEP-NETs [20].

In a recently published study, Skoura and colleagues have investigated the impact of ^{68}Ga-DOTA-TATE PET/CT on imaging on the management of 728 patients with NETs. They showed that the sensitivity, specificity, accuracy, positive-predictive value, and NPV of ^{68}Ga-DOTA-TATE PET/CT were 97, 95.1, 96.6, 98.5, and 90.4%, respectively. A change in the treatment plan was noted in 40.9% of patients, owing mainly to new unexpected findings [21].

Our study showed comparable values of sensitivity and specificity of ^{68}Ga-DOTA-NOC PET/CT to those described in the literature [17,19]. These values were higher than the literature results for dedicated CT, scintigraphy, and ^{18}F-FDG PET/CT [16,20–23].

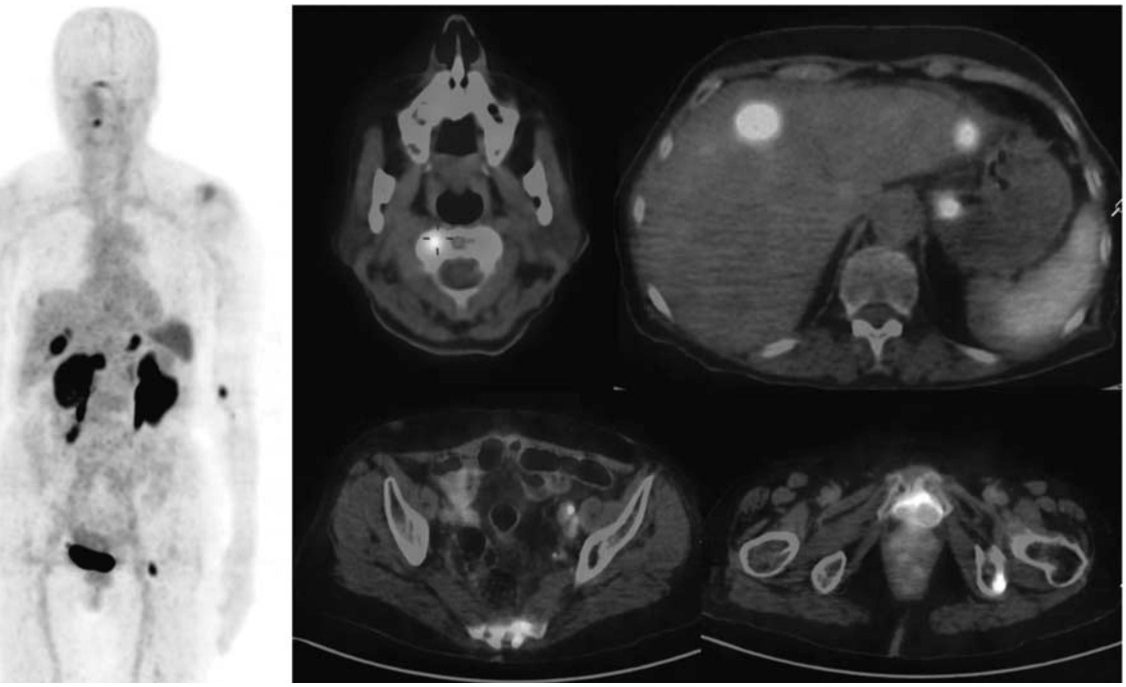
The highest accuracy (0.952) of ^{68}Ga-DOTA-NOC PET/CT was noted in follow-up patients. This can be attributed to the advanced disease in this group of patients who usually present with multiple metastases (Fig. 5).

Most false-negative results were found in the staging group. This can be attributed to the small size of the tumor in this group, which was usually obtained by tissue sampling for example through gastroscopy and colonoscopy. Other false-negative results were attributed to the high grade of the tumor and hence the loss of somatostatin receptor expression. Most patients with a clinical indication alone had a negative scan whereas patients with radiological indication had a high positive result ratio. This indicates that clinical suspicion alone is not enough to justify a ^{68}Ga-DOTA-NOC scan and further biochemical supportive information along with conventional radiological studies should precede the ^{68}Ga-DOTA-NOC study.

Conclusion

PET/CT with ^{68}Ga-DOTA-NOC is a highly sensitive and specific study for NETs that has been proven superior to diagnostic CT and scintigraphy in various clinical situations. This higher sensitivity for tumor detection has a clinical impact in a considerable number of patients, especially compared with CT. Our results support the use of ^{68}Ga-DOTA-NOC PET/CT as a primary diagnostic modality when evaluating NETs. By pooling data from both centers, and by showing that our experience with this exciting radiotracer is very similar, we hope to have further enhanced the acceptance of this radiotracer into routine clinical practice in most

Fig. 5



A 75-year-old woman referred for postsurgical evaluation for a small bowel neuroendocrine tumor. ^{68}Ga-DOTA-NOC PET/CT shows a metastatic neuroendocrine tumor into the liver corresponding to a mild hypodense lesion on CT scan, the bone (cervical spine and pelvis) corresponding to a mild sclerotic lesion on CT scan, with retroperitoneal centimetric active metastatic lymph nodes. CT, computed tomography.

geopolitical settings across the world. We also believe that collaborations such as ours provide reassurance to patients and healthcare planners and a template for a more objective evaluation of tests that are considered complex and expensive. Registries such as ours can provide vital information when planning multicenter trials.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

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