68Ga-DOTANOC PET/CT Clinical Impact in Patients with Neuroendocrine Tumors

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Several authors reported the superiority of 68Ga-DOTANOC PET/CT to conventional imaging (CI) for the assessment of neuroendocrine tumors (NET). However, the detection of a higher number of lesions is not necessarily followed by a modification of disease stage or therapeutic approach. The aim of this study was to assess the impact of 68Ga-DOTANOC PET/CT on the clinical management of NET patients. **Methods:** The study included 90 patients with pathologic confirmation of NET, CT performed within a month of 68Ga-DOTANOC PET/CT, and a follow-up period of at least 1 y. PET/CT results were compared with CI results. As a standard of reference to finally evaluate PET results, clinical and imaging follow-up data were used. To assess the clinical impact of PET findings, all referring physicians were contacted after PET and asked about how patients were managed. Stage or therapy modifications were independently recorded, and the overall impact was evaluated patient by patient if PET results either affected therapy or caused a change in disease stage. **Results:** Considering PET/CT and CI concordant cases (47/90 [52.2%]), PET findings affected the therapeutic management in 17 of 47 (36.2%) patients. Although PET did not result in modification of disease stage, 68Ga-DOTANOC detected a higher lesion number in most patients. PET/CT and CI findings were discordant in 42 of 90 (46.7%) patients: PET resulted in a modification of stage in 12 patients (28.6%) and affected the treatment plan in 32 patients (76.2%). PET and CT were both equivocal in 1 patient (1/90). Considering all cases, 68Ga-DOTANOC PET/CT affected either stage or therapy in 50 of 90 (55.5%) patients. The most frequent impact on management (27 patients) was the initiation or continuance of peptide receptor radionuclide therapy, followed by the initiation or continuance of somatostatin analog medical treatment (7 patients) and referral to surgery (6 patients). PET prevented unnecessary surgery in 6 patients and excluded from treatment with somatostatin analogs 2 patients with NET lesions that did not express somatostatin receptors. Less frequent impacts on management included the initiation of radiotherapy (1 patient), further diagnostic investigation (1 patient), and liver transplantation (1 patient). **Conclusion:** 68Ga-DOTANOC PET/CT either affected stage or caused a therapy modification in more than half the patients, thus confirming the clinical role of PET in the management of NET.

The recent introduction of 68Ga-DOTA-peptide PET/CT for the evaluation of neuroendocrine tumors (NETs) has significantly improved the diagnostic work-up, previously based only on conventional imaging (CI) modalities (ultrasound, CT, endoscopy, MRI) and somatostatin receptor scintigraphy (SRS) (*1,2*). Because of the low cost and wide availability, ultrasound and CT are generally performed as first-line investigations in NET patients. In the past decade, nuclear medicine procedures, such as SRS, have played a central role in the functional assessment of NET. More recently, the development of novel PET tracers (68Ga-DOTA-peptides) specifically binding to somatostatin receptors (SSRs) overexpressed on the surface of NET cells allowed the visualization of NET on 68Ga-DOTA-peptide PET/CT scans. Several different DOTA-peptides (DOTATOC, DOTANOC, and DOTATATE) have been used in the clinical setting for either NET diagnosis or peptide receptor radionuclide therapy (PRRT). The major difference among these compounds relies on a slightly different affinity to SSR subtypes (sst). Although all tracers can bind to sst2—the predominant receptor type in NET—and DOTATOC and DOTANOC also bind to sst5, only DOTANOC presents a good affinity for sst3 (*3*). 68Ga-DOTANOC, compared with similar diagnostic compounds, was also reported to present a favorable dosimetry (*4*).

PET/CT with 68Ga-DOTA-peptides was reported to present a higher sensitivity for the detection of well-differentiated NET than other imaging procedures (particularly CT and SRS) (*5–8*). PET was especially useful in detecting small lesions, particularly at bone and node level (*8*), and in patients with unusual anatomic localization (*9*).

Although the accuracy of 68Ga-DOTA-peptide PET/CT is superior to that of CT, the detection of additional sites of

disease is not necessarily associated with an effect on the therapeutic approach. Therefore, PET findings affect the patient's clinical management only when PET, compared with other imaging procedures, provides additional information. In particular, the detection of unsuspected metastatic disease or local relapse, identification of the occult primary tumor (unknown primary carcinoma [UPC]), or the confirmation or exclusion of SSR expression on tumor cells are all conditions that can modify the therapeutic approach.

The aim of the present study was to evaluate the effect of ^{68}Ga-DOTANOC PET/CT on the clinical management of patients with NET.

MATERIALS AND METHODS

We retrospectively reviewed all patients who underwent ^{68}Ga-DOTANOC PET/CT at the nuclear medicine unit, S. Orsola-Malpighi Hospital, Bologna, Italy, as part of their diagnostic work-up between September 2006 and May 2008. Patients with histologic confirmation of NET, a CT scan performed within a month of the PET scan, and a follow-up period of at least 1 y were included in the study. Overall, 90 patients were enrolled. Detailed clinical history was available for all patients.

^{68}Ga-DOTANOC was synthesized at the radiopharmacy of the nuclear medicine unit. ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga generator, and DOTANOC was labeled with ^{68}Ga following the procedure described by Zhernosekov et al. (10).

PET/CT scans were obtained 60 min after the intravenous injection of about 180 MBq (120–185 MBq) of ^{68}Ga-DOTANOC using a dedicated PET/CT tomograph (Discovery STE or Discovery LS; GE Healthcare) from the skull base to the middle part of the thigh. PET scan emission images were recorded for 4 min per bed position in 2-dimensional mode using the Discovery LS or 3 min per bed position in 3-dimensional mode using the Discovery STE. All images in each scan were corrected for scatter, randoms, dead time, and decay. CT acquisition parameters were 120 kV, 60 mA, 0.8-s tube rotation, and 5-mm thickness; scaled CT images were used to obtain CT attenuation-corrected PET images. Low-dose CT was performed without intravenous contrast enhancement.

Discovery LS images were reconstructed with a 2-dimensional ordered-subset expectation maximization iterative reconstruction algorithm (2 iterations, 28 subsets), and Discovery STE images were reconstructed using a fully 3-dimensional iterative reconstruction algorithm.

PET/CT images were read by 2 experienced nuclear medicine specialists, and the final report was based on the readers' consensus.

Diagnostic CT was performed using a Siemens tomograph (Somatos Sensation Cardiac, 16-slice). CT acquisition parameters were 120 kV and 250 mA. Intravenous contrast was administered in all patients. Precontrast, arterial, and portal-venous abdominal phases were acquired (slice thickness, 0.75 mm for the arterial phase and 1.5 mm for the pancreatic and portal-venous phases; slice spacing, 0.5–1 mm). Arterial phase images were reconstructed to a thickness of 0.75 mm, and pancreatic and venous phase images were reconstructed at 1 mm. In addition to CT, MRI was also performed in 10 paraganglioma patients. The MRI study, using a Signa 1.5-T unit (GE Healthcare), consisted of unenhanced axial, coronal, and sagittal T1-weighted spin-echo images, followed by a turbo spin-echo proton density–weighted sequence, T2-weighted turbo spin-echo images, and finally T1-weighted spin-echo images after an intravenous injection of gadolinium-diethylenetriaminepentaacetic acid (0.1 mmol/kg of Magnevist; Schering). Diagnostic CT and MRI scans were evaluated by 2 experienced radiologists, and the final report was based on the readers' consensus.

Indications to perform PET included staging in 23 of 90 patients (25.5%; in 3 patients, staging was indicated as part of multiple-endocrine neoplasia syndrome), restaging in 36 of 90 (40%), follow-up in 17 of 90 (18.8%), response to PRRT treatment in 4 of 90 (4.4%), unknown primary NET site in 4 of 90 (4.4%), and equivocal CI findings in 6 of 90 (6.6%).

^{68}Ga-DOTANOC PET/CT results were compared with CI results (CT in all patients; MRI was also performed in 10 paraganglioma patients). For the evaluation of PET studies, any area with an intensity greater than background that could not be identified as physiologic activity (pituitary gland, spleen, liver, adrenal glands, head of the pancreas, thyroid, and the urinary tract) was considered to indicate tumor tissue. As a standard of reference to finally evaluate PET results (true-positive, true-negative, false-positive, and false-negative), clinical and imaging follow-up data were used (16 mo; range, 15–18 mo).

To evaluate the clinical impact of PET findings, all referring physicians were contacted after PET and were asked information on how patients were managed and how PET results influenced clinical decisions. Each referring physician was contacted by telephone and asked to retrieve all clinical data on the patients included in the study; clinical data referring to the time before and after the ^{68}Ga-DOTANOC PET/CT scan were recorded. In particular, referring physicians were asked whether the PET result led to any changes in clinical management, such as initiation or exclusion of targeted therapy after the demonstration of presence or lack of SSRs, scheduling of surgery, exclusion of surgical procedures because of the presence of diffuse disease, initiation of radiotherapy or chemotherapy, or use of further diagnostic procedures. Stage or therapy modifications after PET were independently recorded, and the overall impact was evaluated patient by patient if the PET report either changed the stage or affected therapy. Disease was staged according to the classification reported by Rindi et al. (11,12) and Travis et al. (13,14).

RESULTS

Ninety patients (54 men, 36 women; mean age, 58 y; age range, 22–86 y) were enrolled in the study. The clinical and epidemiologic characteristics of the studied population are reported in Table 1.

The primary tumor was most frequently localized at the gastrointestinal level (32 patients), followed by the pancreas (30 patients), lungs (16 patients), and other sites (11 patients). In 1 patient, the primary tumor site remained occult. In 50 of 90 patients, the primary tumor was excised before PET, and in 40 of 90 patients pathologic confirmation was obtained on biopsy specimens from metastatic disease. At pathologic evaluation, the tumor was well differentiated in almost all patients (88), poorly differentiated in 1 patient, and moderately differentiated in 1 patient.

TABLE 1. Patient Clinical and Epidemiologic Characteristics

Characteristic	n
Sex	
F	36
M	54
Age (y)	
Mean	58
Range	22–86
Indication for PET	
Equivocal CI	6
Follow-up	17
Interim PET	4
Restaging	36
Staging	23
UPC	4
Primary tumor site	
Gastrointestinal tract (other than pancreas)	32
Appendix	1
Duodenum	3
Ileum	27
Water papilla	1
Pancreas	30
Lung	16
Paraganglioma	10
Thymus	1
Occult*	1
Pathology	
Well-differentiated NET	88
Moderately differentiated	1
Poorly differentiated	1

*Site of primary tumor remained occult in 1 patient; pathologic examination was performed on metastatic tissue.

Interim PET = PET during therapy.

PET/CT findings (Table 2) were concordant with CI in 47 of 90 patients (52.2%), discordant in 42 of 90 patients (46.7%), and equivocal in 1 patient (1.1%).

Considering PET and CI concordant cases (47/90), PET provided relevant information for therapeutic management in 17 of 47 patients (36.2%). In particular, 68Ga-DOTANOC PET/CT results suggested 12 patients for PRRT (with either 90Y-DOTATOC or 177Lu-DOTATATE) and 2 patients for cold somatostatin analog (SSA) medical treatment. PET showed

TABLE 2. Comparison of 68Ga-DOTANOC PET/CT and CI Findings and Their Impact on Stage or Therapy Modifications

Finding	n	%
PET and CI in concordance	47/90	52.2
PET impact on stage	None	
PET impact on therapy	17/47	36.2
PET and CI in discordance	42/90	46.7
PET impact on stage	12/42	28.6
PET impact on therapy	32/42	76.2
PET and CI equivocal	1	1.1
PET impact	1	100.0

the response to treatment in 2 patients. In 1 patient, PET was performed to exclude the presence of SSR-expressing lesions—other than the ones known at liver level—that would have made the patient ineligible to receive a liver transplant. PET did not affect disease staging in any of the CI-concordant cases, although in most patients PET detected a higher number of lesions.

Discordant 68Ga-DOTANOC PET/CT and CI findings were observed in 42 of 90 patients. PET resulted in a modification of either stage or therapy in 32 patients (76.2%). In particular, stage was modified on the basis of PET results in 12 patients (28.6%). PET upstaged the disease in 5 of 32 patients (identifying new sites of metastatic disease), and in 7 patients PET downstaged the disease: PET results were negative in 5 patients and in 2 patients excluded metastatic disease at liver and nodal levels. In the remaining 20 patients, PET did not change disease stage but determined modification of the therapeutic approach.

Regarding 68Ga-DOTANOC PET/CT impact on therapy management (32 patients [76.2%]) after PET, PRRT was started in 12 patients, PRRT and chemotherapy in 1 patient, SSA medical therapy in 1 patient, and radiotherapy in 1 patient. In 3 patients, PET results confirmed the efficacy of the treatment (cold SSAs in 2 patients and PRRT in 1 patient), which was, therefore, continued. In 2 patients, PET did not demonstrate the presence of SSRs on NET lesions, and these patients were thus excluded from SSA medical therapy.

In 6 patients, PET findings recommended the patients for surgical treatment (in 3 of these 6 patients, the recommendation was based on identification of the site of the unknown primary). In 1 of the 3 UPC patients, PRRT was performed in addition to surgery. Of the remaining 3 of 6 patients who were surgically treated after PET, local relapse was identified in 2 patients and a single liver metastatic site in 1 patient.

PET was truly negative in 6 patients whose results were reported as equivocal (2 patients) or suggestive of relapse (4 patients) at CI. On the basis of the PET report, the patients were not treated further, and clinical follow-up validated PET results.

Although both PET and CI results were inconclusive in 1 patient, PET images showed suggestive findings at the duodenum level, and further diagnostic procedures were recommended. The patient was later investigated with upper gastrointestinal endoscopy, which revealed the presence of a NET duodenal lesion that was subsequently surgically excised.

Considering all cases (Table 3), 68Ga-DOTANOC PET/CT affected either stage or therapy modification in 50 of 90 patients (55.5%). Most frequently, the effect on management was to initiate or continue PRRT (27 patients), followed by the initiation or continuation of SSA medical treatment (7 patients). PET findings recommended 6 patients for surgical treatment: excision of the unknown primary tumor site (3 patients), relapsing disease (2 patients),

TABLE 3. Overall Impact of PET on Clinical Management	
Impact	n
SSA medical therapy started or continued	3/4
SSA medical therapy prevented	2
PRRT started or continued	26*/1
PRRT prevented	0
Radiotherapy started	1
Surgery initiated	6*
Surgery prevented	6
Indication for further diagnostic procedure	1
Indication for liver transplantation	1
Total	51*

*One patient received combined PRRT and surgery based on PET report.

or single liver metastasis (1 patient). PET prevented unnecessary surgery in 6 patients and inefficient treatment with SSAs in 2 patients with NET lesions that did not express SSR. Less frequent conditions included the initiation of radiotherapy (1 patient), further diagnostic investigation (1 patient), and liver transplantation (1 patient).

DISCUSSION

The recent development of ^{68}Ga-DOTA-peptides for PET led to an increasing interest in the use of PET/CT for the assessment of NET (6,15). In this clinical setting, PET has been used both for the diagnosis of disease extent and as a preliminary procedure to evaluate SSR expression before the start of PRRT or cold SSA treatment.

Much emphasis in the literature has been focused on the evaluation of PET sensitivity, specificity, and accuracy, as compared with that of CI (CT, MRI) or nuclear medicine (SRS) procedures in various forms of solid tumors, including NET (7,8,16). However, the detection of a higher number of lesions is not always followed by a change in disease stage and does not always affect therapeutic approach.

Our study showed that ^{68}Ga-DOTANOC PET/CT influenced patients' management in more than half of the studied population. Considering all cases, the major impact of PET findings was on the therapeutic management rather than stage modifications. In fact, although in most patients PET detected a higher number of lesions than did CI, this was followed by a change of disease stage in only a few patients (12/90 [13%]).

The effect of ^{68}Ga-DOTANOC PET/CT on the therapeutic management was particularly evident in patients in which PET and CI were discordant (impact in discordant cases, 76%, vs. impact in concordant cases, 36%). In most patients, the PET effect on therapy was to start or continue PRRT or SSA medical therapy (33/90 [37%]) on the basis of the demonstration of SSR expression. Moreover, PET was also useful in preventing inefficient targeted therapy in 2 patients who lacked SSR expression. Overall, PET

findings on SSR expression affected the clinical management in more than one third of the patients (35/90 [39%]). Therefore, our data support the usefulness of PET with ^{68}Ga-DOTANOC as a preliminary procedure in selecting the patients who could benefit from targeted therapy with either cold or hot SSAs.

It is well known that treatment with SSAs in patients with SSR-expressing lesions is associated with the reduction of signs and symptoms of hormone hypersecretion, improvement of quality of life, and slowing of tumor growth, with a consistent survival benefit (17). In particular, in an Italian multicenter trial cold SSAs (octreotide or lanreotide) were used mainly to obtain symptomatic control of hypersecretory syndromes—with biochemical responses in 73% and 77% of patients, respectively—with only 3% objective responses in carcinoids (18). In a recent paper describing the outcomes of 92 patients with metastatic carcinoid, the median overall survival was almost 2 times longer in patients receiving long-acting SSAs than in untreated patients (112 vs. 53 mo) (19).

Several clinical phase I–II trials indicated that PRRT with radiolabeled SSAs is among the promising newly developed targeted tools in NET (20). Although a large variation in the inclusion criteria, dosage, and treatment scheme and overall antitumor effects was reported between studies (21), treatment with either ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE allows the delivery of high-absorbed doses to tumors expressing sst2 receptors, with partial and complete objective responses in up to 30% of patients (17).

The second most common change in management was either the addition of surgery or exclusion from further therapy. In half the patients who were recommended for surgical treatment, the indication to perform tumor excision followed the visualization of the primary tumor site on the ^{68}Ga-DOTANOC PET/CT scan. It is well known that the identification of the UPC localization is a fundamental prerequisite for optimization of treatment planning, and failure to detect the UPC is characterized by higher mortality (22). Whole-body PET/CT using ^{18}F-FDG has been successfully used for the detection of UPC of the most common malignancies (detection rate, 24%−40%) (23–26). However, to our knowledge only 1 systematic study has evaluated the role of ^{68}Ga-DOTANOC PET/CT for the assessment of UPC in NET patients (27).

In our study population, ^{68}Ga-DOTANOC PET/CT was performed in 1 patient to exclude the presence of disease—which would have prohibited the patient from the liver transplant waiting list—at sites other than the liver. Although performed in a minority of patients, liver transplantation in NET patients with hepatic secondary lesions has been reported to ensure good palliation in highly selected patients: symptomatic patients refractory to systemic medical treatment or unsuitable for interventional procedures and those with a progressive hepatic tumor load (28,29). In patients not meeting these criteria, the risks of surgery-related morbidity and mortality, tumor progression,

and immunosuppressive treatment might favor a conservative approach. Although both SRS and ^{68}Ga-DOTA-peptide PET/CT proved to be valuable preliminary studies before liver transplantation, Frilling et al. encouraged the replacement of SRS with PET in all screening protocols (28).

CONCLUSION

Our data showed that ^{68}Ga-DOTANOC PET/CT provided relevant information for NET patients' clinical management: in our series PET affected the therapeutic approach in more than half the patients. Our results indicate PET as a mandatory procedure to guide treatment planning.

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