Eur J Nucl Med Mol Imaging (2016) 43:432–440
DOI 10.1007/s00259-015-3178-3

ORIGINAL ARTICLE

Molecular response assessed by ^{68}Ga-DOTANOC and survival after ^{90}Y microsphere therapy in patients with liver metastases from neuroendocrine tumours

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Received: 22 May 2015 / Accepted: 14 August 2015 / Published online: 2 September 2015

Abstract
Purpose We investigated the prognostic role of ^{68}Ga-DOTANOC in patients affected by hepatic metastases from neuroendocrine tumours (NET) undergoing ^{90}Y radioembolization (^{90}Y-RE).
Methods A group of 15 consecutive patients with unresectable NET liver metastases underwent ^{68}Ga-DOTANOC PET at baseline and 6 weeks after ^{90}Y-RE. Molecular response was defined as a reduction of >50 % in the tumour-to-spleen ratio (ΔT/S). The patients were divided into two groups (responders with ΔT/S >50 % and nonresponders with ΔT/S <50 %) Patients were followed up by imaging and laboratory tests every 3 months until death or for at least 36 months following ^{90}Y-RE. Statistical analysis was performed to identify factors predicting overall survival (OS) and progression-free survival (PFS).
Results A decrease in T/S ratio was seen in all patients on ^{68}Ga-DOTANOC PET scans performed after ^{90}Y-RE. Nine patients were classified as responders and six as nonresponders. The mean OS in all patients was 31.0 months. Responders had a significantly (p<0.001) longer OS (mean 36.0 ±2.5 months) and PFS (mean 29.7±3.4 months) than nonresponders. In a multivariate analysis, none of the other examined variables including age, unilobar vs. bilobar locations, bilirubin levels, radiological response or the presence of extrahepatic disease significantly predicted patient outcome.
Conclusion Molecular response assessed with ^{68}Ga-DOTANOC PET might be a useful predictor of survival in patients affected by NET liver metastases treated with ^{90}Y-RE.

Keywords ^{68}Ga-DOTANOC · PET/CT · Neuroendocrine tumours · ^{90}Y-Radioembolization

Introduction

Neuroendocrine tumours (NET) are a heterogeneous group of tumours originating from neuroendocrine cells of the digestive and respiratory tracts [1]. The most common site of metastasis is the liver, for which surgery is the most effective therapy, but is often inappropriate due to massive hepatic involvement [2]. Chemotherapy does not offer significant benefits in terms of survival and therapy with somatostatin analogues can control hormone-mediated symptoms but has a poor antitumour effect [3]. Several studies have shown that peptide receptor radionuclide therapy (PRRT) with ^{90}Y-labelled or ^{177}Lu-labelled octreotide analogues can achieve good therapeutic results in NET [4]. However, PRRT has some limitations in treating hepatic lesions. The biodistribution of labelled octreotide analogue includes marked renal uptake and clearance, and around 30 % of the injected activity is lost in the urine within the first few hours and does not contribute to the therapy [5]. ^{90}Y-Radioembolization (RE) has emerged as a valuable therapeutic option in unresectable, chemotherapy-refractory hepatic metastases [6] and has also been successfully used for the treatment of NET liver lesions [7].

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PET/CT is a well-established imaging method in oncology and has been proved to be useful for monitoring the response of tumours treated with ^{90}Y microspheres [8]. However, it is well known that FDG, the radiophamaceutical most commonly used in clinical practice, is not adequate for the imaging well-differentiated NET [9]. To overcome this drawback, a variety of PET tracers have been developed that specifically bind to somatostatin receptors (SSRs) overexpressed on the surface of NET cells, thus allowing PET imaging of NET [10]. It has been reported that ^{68}Ga-DOTA peptides show high sensitivity in detecting well-differentiated NET. There is also growing evidence suggesting that these tracers may be able to deliver prognostic information in NET patients undergoing octreotide treatment or PRRT [11]. Nevertheless, to our knowledge, the potential role of ^{68}Ga-DOTA peptides in assessing the molecular response of hepatic NET in patients treated with ^{90}Y-RE has not yet been investigated.

The aim of this study was to assess the role of early response assessment with ^{68}Ga-DOTA-1-Nal(3)-octreotide (^{68}Ga-DOTANOC) in predicting the final outcome in patients with hepatic NET after ^{90}Y-RE.

Materials and methods

Patients

Enrolled in this study were 15 patients (10 men, 5 women, mean age 60.0±5.4 years) with well-differentiated (G1-/2) unresectable NET hepatic metastases. The enrolment criteria were: histological proof of NET, liver-only or liver-predominant disease, age ≥18 years, ability and willingness to provide written informed consent, life expectancy >3 months, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, bilirubin <2.0 mg/dL, albumin >2.0 g/dL, international normalized ratio (INR) <1.5, creatinine <2.0 mg/dL, platelets ≥100,000/μl, haemoglobin ≥9.0 g/dL, and white blood cells ≥1,500/μl. Patients with predominant extrahepatic disease, active CNS metastases or diffuse peritoneal metastases were excluded.

Pretherapeutic examination

All patients provided written informed consent prior to the procedure and the associated risk. Preprocedural evaluation consisted of: contrast-enhanced CT, ^{68}Ga-DOTANOC PET/CT, liver sonography, and clinical and laboratory examinations. Angiography with selective visceral catheterization was performed to evaluate the vascular and tumour anatomy and blood-flow dynamics, enabling determination of the optimal placement of the catheter for selective treatment. A ^{99m}Tc-macroaggregated albumin scan was performed to test gastrointestinal flow and to estimate the percent of injected activity shunted to the lungs. In addition, baseline CT and PET/CT images were evaluated for the percentage of the liver with tumour involvement and the presence of eventual extrahepatic metastases.

^{90}Y-Radioembolization

After 7 – 10 days the patients returned to our department for the treatment session that was performed by selective catheterization of the main hepatic artery via a transfemoral approach, and embolization of the gastroduodenal and gastric arteries. After selective catheterization of the right/left hepatic artery, a slow manually controlled injection of ^{90}Y microspheres suspended in sterile water alternating with contrast medium for assessing persisting anterograde arterial flow was administered to the patient without sedation over about 30 min under intermittent fluoroscopic guidance. Resin spheres (SIR-Spheres; Sirtex Medical, Sydney, Australia) were administered in all patients. The prescribed ^{90}Y activity was calculated as the patient-specific activity according to the manufacturer's vial applying using the body surface area (BSA) formula [12]. All the patients with bilobar metastases were treated with separate sequential lobar ^{90}Y administrations with 6 weeks between the two procedures.

PET imaging

^{68}Ga-DOTANOC was synthesized in the radiopharmacy of the nuclear medicine unit. ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga generator, which was connected to an automated PC-controlled radiopharmaceutical labelling device (EluSynthGa68; IASON, Graz-Seiersberg, Austria). The PET/CT scan was performed 60 min after intravenous administration of 150 MBq (±30 %) of ^{68}Ga-DOTANOC. A Gemini PET/CT system (Philips Healthcare, Best, The Netherlands) was used that combines a third-generation multislice spiral CT scanner (low-dose, 16-slice, 100 mAs) and a dedicated full-ring PET scanner. The PET and CT devices were mechanically aligned back to back and shared a table. PET images were acquired in three-dimensional mode using a matrix of 128× 128 pixels. PET images were reconstructed using ordered subsets expectation maximization (two iterations and eight subsets). Proper registration of images was ensured by shared positional information on the table and the patient for both the CT and the PET acquisitions. Data obtained from the CT scan were used for attenuation correction of the PET data and for fusion with attenuation-corrected PET images to integrate physiological and anatomical images.

Assessment of response

All subjects underwent ^{68}Ga-DOTANOC PET before the procedure. If the lesion uptake was higher than that of the

surrounding hepatic parenchyma, the lesion was classified as DOTANOC-positive. Standardized uptake values (SUV) were calculated using regions of interest (ROI). In each patient, up to three hepatic metastases with the highest maximum SUV (SUVmax) were selected as the target lesions and the normal spleen parenchyma as the background control. In order to normalize tumour SUVs the ratio of SUVmax of the tumour lesion to the mean SUV of the normal spleen parenchyma (SUVmean), the tumour-to-spleen (T/S) ratio, was calculated.

In order to reduce potential partial volume effects, the reference ROIs in the spleen were drawn with a diameter of 2 cm. Six weeks after the ^{90}Y-RE, patients underwent ^{68}Ga-DOTANOC PET to assess the early molecular response to the procedure. The follow-up PET/CT scan was compared with the pretreatment scan and the relative change in T/S ratio (ΔT/S) was determined. Molecular response was defined as a reduction of >50 % in ΔT/S. The patients then resumed a routine 3-monthly schedule of laboratory tests and imaging (^{68}Ga-DOTANOC PET, contrast-enhanced CT) until the primary endpoint (death) or for at least 36 months in long-term survivors. The response of the primary tumour to ^{90}Y-RE was evaluated from the CT images using modified Response Evaluation Criteria in Solid Tumors (mRECIST) [13].

^{90}Y PET imaging

All patients underwent a PET scan to evaluate the microsphere distribution pattern [14].

Tumour markers

The normal physiological ranges were considered less than 94 ng/mL for chromogranin A (CgA). In patients with elevated pretherapeutic CgA, the percentage change after therapy was calculated. A decrease of more than 50 % or within the reference range was considered significant indicating a response.

Statistics

The primary endpoint was overall survival (OS), defined as time from ^{90}Y-RE until death. The secondary endpoint was progression-free survival (PFS), defined as the time from ^{90}Y-RE to disease progression. PFS and OS were calculated using the Kaplan-Meier method (MedCalc 11.3.8.0; MedCalc Software, Mariakerke, Belgium). The Kaplan-Meier method was also used to analyse differences in OS and PFS, and Cox analysis was used to identify prognostic factors. Significance was established at the level of $p<0.05$.

Results

Patients and tumour characteristics

The clinical features of the patients and their final outcome after ^{90}Y-RE are summarized in Table 1. The primary NET sites were the small bowel in 12 patients, the pancreas in 2 patients, and the bronchus in 1 patient. All patients had a percentage of the liver with tumour involvement less than 25 %. Of the 15 patients, 8 showed elevated pretherapeutic CgA values. Four subjects were affected with functional syndrome due to hormone secretion, and in these patients PET was performed just (1 – 3 days) prior to the scheduled monthly dose of long-acting octreotide.

All 15 patients showed ^{68}Ga-DOTANOC uptake within the hepatic lesions on the pretreatment PET scan, and 11 of the 15 showed unilobar locations and 4 multiple bilobar metastases. Of the 15 patients, 12 had exclusively hepatic disease, and 3 had extrahepatic locations (2 abdominal lymph nodes, 1 bone metastases). No patients were found to have a significant hepatopulmonary shunt. The average administered activity of ^{90}Y-spheres was 1.6±0.19 GBq fwith a total of 11 unilobar ^{90}Y administrations and 4 sequential bilobar treatments.

Assessment of response

According to mRECIST, seven patients showed a partial response (PR) and eight had stable disease (SD). A decrease in ΔT/S was found in all patients on the ^{68}Ga-DOTANOC PET scan performed 6 weeks after ^{90}Y-RE. Nine patients were classified as responders (Fig. 1) and six as nonresponders (Fig. 2). All patients with functional syndrome were responders and had complete symptomatic remission.

^{90}Y PET imaging

No extrahepatic sites of ^{90}Y microsphere uptake were recorded.

Tumour markers

Among the eight patients with elevated CgA, three showed a significant decrease in tumour marker levels.

Statistical analysis and clinical outcome

The mean OS in all patients was 31.0 months (95 % CI 26.9 – 35.0 months). Subjects with a ΔT/S >50 % and ΔT/S <50 % had a mean OS of 36.0±2.5 months and 23.6±5.3 months, respectively ($p<0.001$). The Kaplan-Meier survival curve in relation to ΔT/S is shown in Fig. 3. The mean PFS in all patients was 24.8 months (95 % CI 21 – 32 months). Subjects with a ΔT/S >50 % and ΔT/S <50 % had a mean

Table 1 Clinical features of the patients and their final outcome after ^{90}Y radioembolization

Patient no.	Age (years)	Sex	Primary NET site	Distribution	Tumour load (%)	Bilirubin at baseline (mg/dL)	CgA at baseline (ng/mL)	Extrahepatic disease	Administered activity (GBq)	CgA decrease	ΔT/S (%)	Molecular response	RECIST response	Progression-free survival (months)	Overall survival (months)
1	55	M	Small bowel[a]	Bilobar	20	0.9	262	None	1.7	S	75.4	R	PR	33	38
2	55	F	Small bowel	Unilobar	17	0.7	Not elevated	None	1.5	–	65.8	R	PR	27	35
3	58	M	Small bowel[a]	Unilobar	22	1.2	386	Abdominal nodes	1.9	NS	84.5	R	PR	33	39
4	65	F	Bronchus	Unilobar	16	0.8	Not elevated	None	1.6	–	41.8	NR	SD	21	28
5	65	M	Small bowel	Unilobar	18	0.7	168	None	1.7	NS	32.0	NR	SD	9	14
6	64	F	Pancreas	Bilobar	23	1.1	247	Abdominal nodes	1.3	NS	65.1	R	PR	33	37
7	48	M	Small bowel	Unilobar	20	0.6	172	None	1.7	NS	25.6	NR	SD	18	27
8	58	M	Small bowel	Unilobar	21	1.4	Not elevated	Bone lesions	1.6	–	59.7	R	SD	27	32
9	52	M	Pancreas	Unilobar	17	1.5	235	None	1.8	NS	24.6	NR	SD	18	23
10	64	F	Small bowel[a]	Bilobar	19	0.8	883	None	1.4	S	88.3	R	PR	32	39
11	61	M	Small bowel	Unilobar	20	0.9	Not elevated	None	1.5	–	45.1	NR	SD	21	28
12	64	M	Small bowel[a]	Unilobar	16	1.3	371	None	1.2	S	77.6	R	PR	32	37
13	58	F	Small bowel	Bilobar	22	1.0	Not elevated	None	1.6	–	33.6	NR	SD	15	22
14	62	M	Small bowel	Unilobar	18	0.9	Not elevated	None	1.8	–	62.4	R	SD	27	33
15	58	M	Small bowel	Unilobar	20	1.1	Not elevated	None	1.7	–	73.4	R	PR	24	34

S significant, *N* non significant, *ΔT/S* decrease in tumour-to-spleen ratio, *R* responders, *NR* nonresponders, *PR* partial response, *SD* stable disease

[a] Patients with functional syndrome

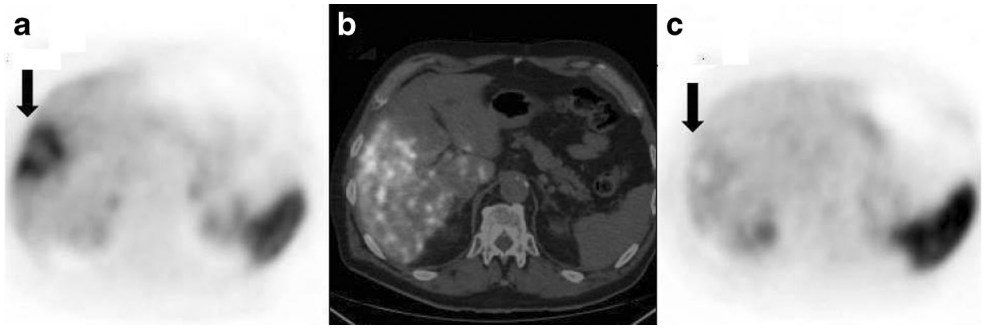

Fig. 1 **a** ^{68}Ga-DOTANOC PET axial slice acquired before treatment shows intense tracer accumulation in a patient with a gross lesion of the right hepatic lobe (*arrow*). **b** Fused unenhanced CT slice and ^{90}Y PET transaxial slice acquired 2 h after administration of ^{90}Y microspheres shows accumulation of spheres in the tumour mass with a necrotic core surrounded by a hot circular region. **c** ^{68}Ga-DOTANOC PET axial slice acquired 6 weeks after the procedure shows a significantly less intense tumour uptake (*arrow*) consistent with a molecular response (ΔT/S was 73.4 %). Overall survival was 34 months

PFS of 29.7±3.4 months and 17.5±4.8 months, respectively ($p<0.001$).

Among the examined variables, both molecular response and mRECIST response had a significant impact on patient survival in the Kaplan-Meier survival analysis (Table 2). In the multivariate analysis, molecular response (i.e. ΔT/S) remained the only independent predictor of both PFS ($p=0.03$, HR=0.92, 95 % CI 0.85 – 0.99) and OS ($p=0.015$, HR=0.86, 95 % CI 0.77 – 0.975).

At the time of the final survival analysis (November 2014), five patients (33.3 %) remained alive and ten patients (66.6 %) had died of their disease.

Toxicities

Immediate complications such as nausea and mild abdominal pain were recorded in seven patients during the 10 h following ^{90}Y-RE. Routine medications led to complete remission of these symptoms. Late complications consisted of moderate gastritis (grade 2) in two patients and moderate cholecystitis (grade 2) in one patient.

Discussion

To the best of our knowledge, this the first study addressing the prognostic role of molecular response assessed with ^{68}Ga-DOTANOC PET in patients with hepatic NET treated with ^{90}Y-RE. Liver metastases are the most crucial prognostic factor in patients with NET, irrespective of the primary site. In patients with unresectable lesions, selection of the optimum treatment is of the utmost importance to improve quality of life and prolong survival [15]. In this regard, there is a growing amount of data concerning the utility of ^{90}Y-RE in NET patients with predominant liver disease and low hepatic tumour burden [7, 16, 17]. King et al. evaluated ^{90}Y-RE in 34 patients with hepatic NET [15]. A symptomatic response was seen in 50 % of the patients at 6 months after treatment, and the mean OS was 29.4±3.4 months. Our results are substantially in agreement with those reported by King et al., although the OS in our cohort was slightly higher probably due to the relatively low hepatic tumour involvement (i.e. <25 % in all patients). The largest retrospective study reported to date in a cohort of 148 patients with hepatic NET undergoing ^{90}Y-RE in a primarily salvage setting showed a median survival of

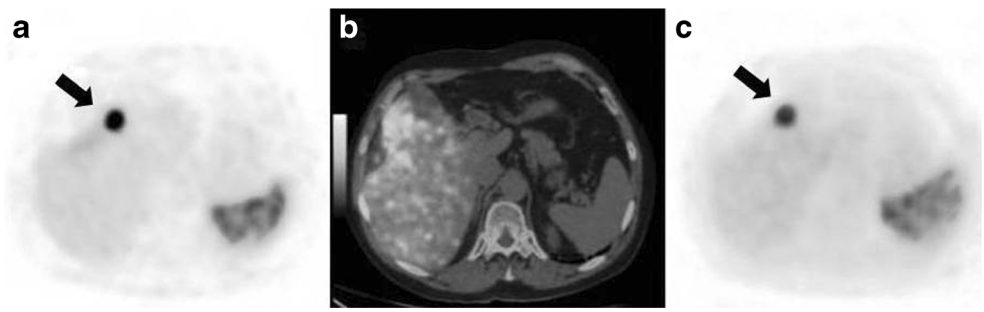

Fig. 2 **a** ^{68}Ga-DOTANOC PET axial slice acquired before treatment shows intense tracer accumulation in a patient with a lesion of hepatic segment IV (*arrow*). **b** Fused unenhanced CTslice and ^{90}Y PET transaxial slice acquired 2 h after administration of ^{90}Y microspheres shows accumulation of spheres in the tumour mass. **c** ^{68}Ga-DOTANOC PET/CT axial slice acquired 6 weeks after the procedure shows substantially unchanged tumour uptake (*arrow*), consistent with no response (ΔT/S was 24.6 %). Overall survival was 23 months

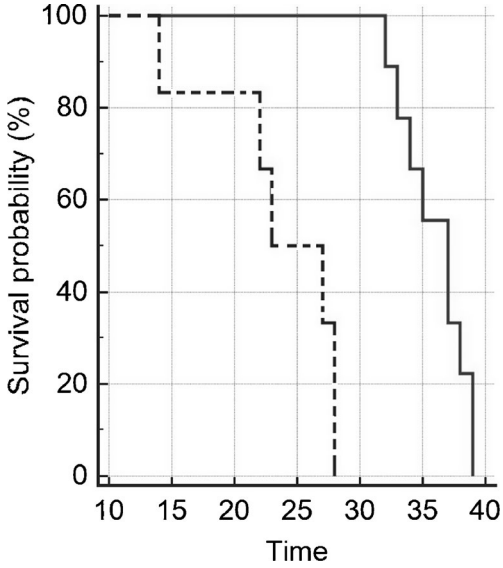

Fig. 3 Kaplan-Meier survival analysis in relation to ΔT/S measured 6 weeks after ^{90}Y radioembolization. Patients with ΔT/S<50 % (*dashed line*) had significantly lower (p<0.001) survival than those with ΔT/S >50 % (*solid line*)

70 months with a response rate of 63 %, with the most of the deaths due to progression of extrahepatic disease [17]. However, the authors collected data from ten different clinical centres, and functional assessment of the responses to therapy was performed in only some of the institutions.

RECIST are widely used to evaluate hepatic malignancies after locoregional treatments [18]. Nevertheless, this morphological approach has some limitations due to confounding factors such as the development of necrotic, oedematous or haemorrhagic changes after ^{90}Y-RE, that may cause paradoxal increases in the dimensions of responding lesions [19]. According to mRECIST, in our series seven patients had PR and eight SD, and thus CT showed a lower response detection rate than molecular imaging. These results are in agreement with those recently reported by Peker et al. [20], indicating that imaging methods reflecting metabolic activity or cellularity, such as diffusion-weighted MRI, may be preferred for the evaluation of NET liver metastases after ^{90}Y-RE.

Table 2 Kaplan-Meier analysis and factors potentially predicting overall survival

	No. of patients	Overall survival (months), mean (95 % CI)	p value
Age (years)			
<60	8	28.6 (22.6 – 34.6)	0.44
>60	7	33.8 (30.5 – 37.1)	
Distribution			
Unilobar	11	30.0 (25.7 – 34.2)	0.20
Bilobar	4	34.0 (26.1 – 41.8)	
Extrahepatic disease			
No	12	29.8 (25.5 – 34.1)	0.25
Yes	3	36.0 (31.9 – 40.0)	
Blirubin at baseline (mg/dL)			
<1	9	29.3 (24.1 – 34.5)	0.46
>1	6	33.6 (29.0 – 38.2)	
mRECIST response			
Partial response	7	37.0 (35.2 – 38.7)	<0.001
Stable disease	8	25.8 (20.6 – 30.9)	
Molecular response			
ΔT/S >50 %	9	36.0 (34.3 – 37.6)	<0.001
ΔT/S <50 %	6	23.6 (19.3 – 27.9)	

ΔT/S decrease in tumour-to-spleen ratio

Several studies [21, 22] have indicated that SSR scintigraphy (SRS) with ^{111}In-diethylene triamine pentaacetic acid octreotide (pentetreotide) may be useful for improving the detection and management of NET. The main drawback of SRS (also when performed with SPECT) is its relatively low spatial resolution and the absence of precise anatomical information. On the other hand, it has been reported that PET/CT with ^{68}Ga-DOTA peptides may be a useful tool for imaging NET [23]. Preclinical studies have demonstrated that radiogallium-labelled peptides show significantly higher and receptor-mediated uptake in SSR-positive tumours in comparison with ^{111}In-pentetreotide [24]. Furthermore, all PET scanners are combined with multislice CT that provides precise anatomical correlation.

Hofman et al. [25] evaluated the role of ^{68}Ga-DOTA-DPhe1-Tyr3-octreotate (DOTATATE) in a cohort of 52 patients with NET. They found that 88 % of the PET studies were abnormal and ^{68}Ga-DOTATATE, when compared with conventional SRS, provided additional information in 83 % of the patiens and consequently had a high impact on management. These results might be explained not only by the higher resolution of PET than of SPECT, but also by the higher affinity of the octreotate for SSRs. Since ^{68}Ga-DOTANOC has a chemical structure similar to that of ^{111}In-pentetreotide, it has been hypothesized that ^{68}Ga-DOTATATE might be more sensitive than DOTANOC for the visualization of SSR-positive tumours. Kabasakal et al. [26] compared ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE for the detection of NETs in 20 patients who had two consecutive PET studies with both tracers. The authors demonstrated that the two ^{68}Ga-labelled tracers are equally accurate for the diagnosis of NET lesions, although ^{68}Ga-DOTATATE was found to have higher lesion uptake.

In a recently published study, Sharma et al. [27] investigated the potential value of ^{68}Ga-DOTANOC PET in a large and exclusive population of patients with NET. The authors analysed data from 141 patients who underwent PET/CT for diagnosis/staging or restaging of pancreatic NET, and found that ^{68}Ga-DOTANOC PET was accurate for both for staging and restaging of NETs. These results are substantially in agreement with ours: ^{68}Ga-DOTANOC was able to correctly characterize NET hepatic lesions before and after administration of the ^{90}Y spheres.

However, there are still limited data regarding the potential usefulness of SSR imaging in the evaluation of patients with NET liver metastases. In this regard, Ezziddin et al. [28] retrospectively assessed a consecutive cohort of 23 patients with hepatic NET undergoing ^{90}Y-RE as salvage therapy after PRRT. Responses were assessed 3 months after the procedure using RECIST, and restaging was supplemented with SSR imaging with ^{111}In-pentetreotide or ^{68}Ga-DOTA-D-Phe1-Tyr3-octreotide (DOTATOC). However, changes in SUV or SUV-derived parameters (such as the tumour-to-liver ratio, T/L ratio) were not taken into account or correlated with the final outcome. Early prediction of response to treatment in tumours is of the utmost importance to guide therapy and limit side effects. Although PET imaging with ^{68}Ga-labelled peptides is a well-standardized procedure for the staging of NET, its utility in predicting treatment response is widely discussed.

Gabriel et al. [29] found no advantage to using ^{68}Ga-DOTATOC over conventional imaging (CT or MRI) in the evaluation of treatment response after completion of PRRT. In particular, SUV analysis of individual lesions was found to be of no additional value in predicting patient responses to therapy. However, it is well known that SUV measurements can be affected by many issues, such as the reconstruction algorithm, the scanner used, the interval between tracer injection and the acquisition, and the partial volume effect [30]. On the other hand, Haug et al. found a significant prognostic impact of SSRs imaging with ^{68}Ga-DOTATATE in 33 patients with well-differentiated NET evaluated at baseline and 3 months after the first cycle of PRRT [31]. Patients with a decrease in tumour-to-spleen SUV ratio had a significantly longer survival than those with a stable or increased score. In addition, the authors found no significant correlation between changes in CgA after treatment and patient outcome. Our results confirm that the serum CgA level may be inappropriate for assessing responses to palliative therapy in patients with well-differentiated NET.

More recently, Kratochwil et al. investigated the value of ^{68}Ga-DOTATOC PET for predicting the outcome in patients with hepatic NET after PRRT [32]. The authors determined SUVmax, T/L ratio and T/S ratio in 30 patients at baseline, and found that these PET-derived parameters correlated with morphological and size changes observed on contrast-enhanced CT after treatment. ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC have similar properties: they both bind SSR subtype 2, although the latter is able also to bind subtype 3 SSR and has more favourable dosimetry [32]. In agreement with previous studies [32, 33], we determined the ratio between the SUV of the liver metastases relative to the spleen uptake for monitoring molecular response of hepatic NET to ^{90}Y-RE. Since the liver itself is the target of the radiembolization, we hypothesized that the spleen might be a more suitable normal background than the liver for normalization in our patient cohort.

It is worth noting that ^{68}Ga-DOTANOC reflects the overexpression of SSRs but does not provide any information on growth rate, metabolism or volume. Recent studies have demonstrated that FDG PET-derived volumetric indices, such as metabolic tumour volume and total lesion glycolysis, may allow the accurate prediction of patient outcome after ^{90}Y-RE [34]. In this regard, a volumetric index obtained using the SUVmax cut-off value of 10 (i.e. VOI_{10SUV})to separate normal liver parenchyma from metastases on ^{68}Ga-DOTANOC PET images has recently been introduced for the volumetric monitoring of NET response to PRRT [35]. A volumetric assessment may provide a more complete and accurate evaluation of molecular response, but the calculation of ΔVOI_{10SUV} is quite time-consuming and requires dedicated workstations. T/S is easy to calculate and might be applied in clinical practice for the stratification of NET patients treated with ^{90}Y-RE.

The main limitation of this study was the relatively small number of patients. However, NET are relatively rare malignancies and ^{90}Y-RE is performed in few institutions, since it is a high-cost therapy and requires a skilled multidisciplinary team. Further studies with larger cohorts collecting data from different sites are needed to confirm our preliminary data.

Conclusion

^{68}Ga-DOTANOC PET is a useful diagnostic tool for evaluating patients with NET liver metastases treated with ^{90}Y-RE. ^{68}Ga-DOTANOC uptake reflects the overexpression of SSRs and thus might be used to differentiate viable neuroendocrine tumour tissue from necrosis/oedema after treatment. PET/CT provides precise anatomical localization and allows the calculation of several semiquantitative parameters. Our results indicate that the assessment of molecular response by ^{68}Ga-DOTANOC PET/CT may be feasible as early as 6 weeks after ^{90}Y-RE; furthermore, ΔT/S might be a useful predictor of survival in patients with NET hepatic metastases undergoing ^{90}Y-RE.

Compliance with ethical standards

Funding None.

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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