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ORIGINAL ARTICLE

Comparison of sequential planar ^{177}Lu-DOTA-TATE dosimetry scans with ^{68}Ga-DOTA-TATE PET/CT images in patients with metastasized neuroendocrine tumours undergoing peptide receptor radionuclide therapy

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Abstract
Purpose The aim of the study was to compare sequential ^{177}Lu-DOTA-TATE planar scans (^{177}Lu-DOTA-TATE) in patients with metastasized neuroendocrine tumours (NET) acquired during peptide receptor radionuclide therapy (PRRT) for dosimetry purposes with the pre-therapeutic ^{68}Ga-DOTA-TATE positron emission tomography (PET)/CT (^{68}Ga-DOTA-TATE) maximum intensity projection (MIP) images obtained in the same patients concerning the sensitivity of the different methods.
Methods A total of 44 patients (59±11 years old) with biopsy-proven NET underwent ^{68}Ga-DOTA-TATE and ^{177}Lu-DOTA-TATE imaging within 7.9±7.5 days between the two examinations. ^{177}Lu-DOTA-TATE planar images were acquired at 0.5, 2, 24, 48 and 72 h post-injection; lesions were given a score from 0 to 4 depending on the uptake of the radiopharmaceutical (0 being lowest and 4 highest). The number of tumour lesions which were identified on ^{177}Lu-DOTA-TATE scans (in relation to the acquisition time after injection of the therapeutic dose as well as with regard to the body region) was compared to those detected on ^{68}Ga-DOTA-TATE studies obtained before PRRT.
Results A total of 318 lesions were detected; 280 (88%) lesions were concordant. Among the discordant lesions, 29 were ^{68}Ga-DOTA-TATE positive and ^{177}Lu-DOTA-TATE negative, whereas 9 were ^{68}Ga-DOTA-TATE negative and ^{177}Lu-DOTA-TATE positive. The sensitivity, positive predictive value and accuracy for ^{177}Lu-DOTA-TATE as compared to ^{68}Ga-DOTA-TATE were 91, 97 and 88%, respectively. Significantly more lesions were seen on the delayed (72 h) ^{177}Lu-DOTA-TATE images (91%) as compared to the immediate (30 min) images (68%). The highest concordance was observed for bone metastases (97%) and the lowest for head/neck lesions (75%). Concordant lesions (n=77; mean size 3.8 cm) were significantly larger than discordant lesions (n=38; mean size 1.6 cm) (p<0.05). No such significance was found for differences in maximum standardized uptake value (SUV_{max}). However, concordant liver lesions with a score from 1 to 3 in the 72-h ^{177}Lu-DOTA-TATE scan had a lower SUV_{max} (n=23; mean 10.9) than those metastases with a score of 4 (n=97; mean SUV_{max} 18) (p<0.05).
Conclusion Although ^{177}Lu-DOTA-TATE planar dosimetry scans exhibited a very good sensitivity for the

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detection of metastases, they failed to pick up 9% of lesions seen on the ^{68}Ga-DOTA-TATE PET/CT. Three-dimensional dosimetry using single photon emission computed tomography/CT could be applied to investigate this issue further. Delayed (72 h) images are most suitable for drawing regions of interest for dosimetric calculations.

Keywords ^{177}Lu-DOTA-TATE · Dosimetry scan · ^{68}Ga-DOTA-TATE · Neuroendocrine tumour

Introduction

Neuroendocrine tumours (NET) are rare neoplasms that secrete peptides and neuroamines. They can cause distinct clinical syndromes, including carcinoid syndrome, but many are clinically silent until late presentation with mass effect [1]. Most NET express a high density of somatostatin receptors, mainly subtype 2, which eventually get internalized after ligand binding [2]. These characteristics allow imaging by somatostatin receptor scintigraphy (typically with ^{111}In-labelled pentetreotide or ^{99m}Tc-labelled somatostatin analogues) as well as peptide receptor radionuclide therapy (PRRT).

^{68}Ga-DOTA-TATE, a selective somatostatin receptor subtype 2 positron emission tomography (PET) radiotracer [3], is an emerging diagnostic tool for effectively identifying primary tumours and for assessing the extent of the disease with high spatial resolution [4–7]. The maximum standardized uptake value (SUV_{max}) of tumour lesions on ^{68}Ga-DOTA-TATE PET/CT has recently been shown to correlate with the receptor density [8, 9].

Treatment should be highly individualized based on NET characteristics, previous therapies and general health status of the patient. PRRT with ^{177}Lu-DOTA-TATE has proven to be an effective and safe therapy option [10–15]. ^{177}Lu has a half-life of 6.7 days and emits both beta radiation of 497 keV (78%) and gamma radiation of 208.3 keV (11%), allowing imaging and dosimetry after therapy. Dosimetry calculations for PRRT are usually performed using ^{177}Lu-DOTA-TATE whole-body planar scans (^{177}Lu-DOTA-TATE) acquired during PRRT.

The purpose of this study was to compare ^{177}Lu-DOTA-TATE dosimetry (planar) scans acquired during PRRT in metastasized NET with ^{68}Ga-DOTA-TATE PET/CT maximum intensity projection (MIP) images to find the sensitivity of the two different methods for the detection of metastases, which could have consequences for answering the question of whether all the lesions seen on PET/CT are taken into consideration for tumour dosimetry calculations.

Materials and methods

Patients

We retrospectively reviewed 44 consecutive patients (30 male, 14 female aged 23–83 years, mean 59±11 years) with histologically proven NET (31 gastroenteropancreatic NET, 6 pulmonary carcinoids, 2 cases of medullary thyroid cancer, 1 renal NET and 4 cases of metastatic NET of unknown primary) (Table 1). All of the patients were enrolled at the Department of Nuclear Medicine/PET Centre, Bad Berka, Germany, where the whole study was performed. They were all referred for PRRT with ^{177}Lu-DOTA-TATE due to progressive disease after failure of other treatment modalities. All patients underwent examinations with ^{68}Ga-DOTA-TATE and ^{177}Lu-DOTA-TATE within 7.9±7.5 days between the studies. The patients did not receive any additional therapy in between the two scans.

Radiochemistry

The radiopharmaceuticals were prepared in the radiopharmacy of the Zentralklinik Bad Berka (Bad Berka, Germany).

Preparation of ^{68}Ga-DOTA-TATE The elution of ^{68}Ga from the ^{68}Ge/^{68}Ga generator (obtained from Eckert and Ziegler, Berlin, Germany) as well as its labelling and associated quality control were performed as described in a previous publication [16]. ^{68}Ga labelling of DOTA-TATE was performed following the procedure described by Meyer et al. [17]. The processed and eluted ^{68}Ga fraction was directly transferred to solutions containing 30–50 μg of DOTA-TATE. Labelling yields of >95% were achieved within 10 min. Overall yields reached 70% at 20 min after generator elution relative to the eluted ^{68}Ga activity, not corrected for decay.

Preparation of ^{177}Lu-DOTA-TATE The ^{177}Lu labelling of the DOTA-peptides was performed as previously described [18]. Briefly, a solution of 500 μg of 2.5-dihydroxybenzoic acid and 20 μg of the corresponding DOTA-peptide in 50 μl of 0.4-M sodium acetate buffer (pH, 5.5) was added to a solution of 1 GBq of ^{177}Lu in 30 μl of 0.05-M HCl. The mixture was heated to 90°C for 30 min and then diluted with 0.9% saline solution, followed by a sterile filtration. Quality control was performed by RP-18 HPLC, solvent A: water, solvent B: acetonitrile (both with 0.1% trifluoroacetic acid), gradient: 0–2 min 95% A, 20 min 95% B, flow rate: 1.2 ml/min, column: LiChrospher 100 RP-18 EC-5 μm 250×4 mm. The radiochemical purity was always greater than 99%. Samples were taken for sterility and pyrogenicity testing.

Table 1 Patient characteristics

Characteristic	Value
Age	59±11
Male to female ratio	30:14
Primary tumour	Total, *n*=44
	Pancreas, *n*=14
	Ileum/jejunum/duodenum, *n*=13
	Rectum/colon, *n*=4
	Lungs, *n*=6
	Thyroid, *n*=2
	Renal, *n*=1
	CUP, *n*=4
WHO classification (*n*=17)	Well-differentiated, *n*=15
	Moderately differentiated, *n*=1
	Poorly differentiated, *n*=1
	Not available, *n*=27
Ki-67 (*n*=22)	High-grade (Ki-67>20%), *n*=4
	Low-grade (Ki-67<2%), *n*=9
	Intermediate-grade (Ki-67: 3–20%), *n*=9
	Not available, *n*=22
Mean dose injected of ^{177}Lu-DOTA-TATE	6,734±936 MBq
Mean dose injected of ^{68}Ga-DOTA-TATE	120.5±11.7 MBq (range 87–144)
Mean time between injection and PET/CT acquisition	83.3±20.3 min (range 60–140)
Number of lesions studied	*n*=318
Mean tumour uptake of ^{68}Ga-DOTA-TATE (SUV_{max})	12.05±8.65
Patients with metastasized NET	Total, *n*=42
	Liver, bone and lymph nodes, *n*=10
	Liver and lymph nodes, *n*=7
	Liver and bone, *n*=4
	Liver, *n*=10
	Others, *n*=11

CUP carcinoma of unknown primary

Imaging

^{68}Ga-DOTA-TATE PET/CT All ^{68}Ga-DOTA-TATE PET/CT scans were accomplished using a dedicated hybrid PET/CT, a camera combining a PET unit and a two-slice CT unit (Biograph Duo, Siemens Medical Solutions). The patients were advised to stop the long-acting formulation octreotide therapy 4–6 weeks before the PET/CT examination. The patients fasted for at least 6 h before the image acquisition and were asked to drink 1.5 l of water-equivalent oral contrast dispersion (Gastrografin). This dispersion is used routinely in PET/CT without known adverse side effects to the accumulation of ^{68}Ga-DOTA-TATE. Whole-body examinations (brain to mid-thigh) were performed with the patient in a supine position with arms raised.

Starting 60 min after an intravenous injection of approximately 100 MBq of ^{68}Ga-DOTA-TATE (containing 5–10 μg of DOTA-TATE peptide for 100 MBq ^{68}Ga), a contrast-enhanced CT was acquired in the craniocaudal direction with a 30-s delay (administration of 100 ml of intravenous contrast by an automated injection pump). CT was performed in spiral mode using a continuous acquisition at 130 kVp, 115 mAs, 4-mm collimation, 5-mm slice width, a table feed of 8 mm per rotation at 0.8-s rotation time and 2.4-mm slice spacing. During the CT, our protocol uses a limited breath-hold technique: patients are asked to hold their breath in normal expiration only for the time that the CT takes to cover the lower lung and liver, which is typically less than 15 s.

Immediately after acquisition of the CT, a PET emission scan was performed without changing the patient's position, starting in the caudocranial direction with the bladder/pelvis region being scanned first. Emission data were acquired at 7–8 bed positions for 1–3 min at each position (depending upon the patient's weight and height) resulting in a total emission scan of no more than 24 min and a total PET/CT examination time of about 30 min (including patient positioning, CT and PET imaging).

^{177}Lu-DOTA-TATE dosimetry whole-body scans ^{177}Lu-DOTA-TATE dosimetry whole-body scans were obtained after intravenous injection of a therapeutic dose with a mean injected activity of 6,734±936 MBq of ^{177}Lu-DOTA-TATE (containing ~150 mg of DOTA-TATE peptide for 7.5 GBq ^{177}Lu) under a nephroprotection regime [19]. For kidney protection, an infusion of 1,500 ml of a combination of lysine and arginine (Lys-Arg) was used; 500 ml of L-lysine HCl 5% plus 250 ml of L-arginine HCl 10% plus 250 ml of saline were mixed and brought to a pH of 7.4. The osmolarity of this solution was 400 mosmol/l, and it contained 25 g of lysine and 25 g of arginine. The infusion was started 30 min before the administration of the therapeutic dose and was continued for 4 h. The radiopharmaceutical was coadministered over 10–15 min by using a second infusion pump system. As reported, the coinfusion of amino acids reduces renal exposure and allows for higher absorbed doses to reach tumours [19]. Imaging was performed at 30 min (immediate) to 2 (early), 24, 48 and 72 h (delayed) post-injection (MedisoMedical Imaging Systems, Budapest, Hungary, X-RING and SPIRIT DH-V

gamma camera; MeGP collimator; peak at 208 keV; 15% energy window; 15 cm/min).

Image interpretation

Images were independently visually interpreted on a HERMES workstation by two experienced nuclear medicine physicians. Images acquired at different time points on ^{177}Lu-DOTA-TATE and ^{68}Ga-DOTA-TATE MIP images were visually inspected in varying scales. In ^{177}Lu-DOTA-TATE images, each focal, abnormal tracer uptake was recorded by anatomical localization and by an intensity uptake score following a 5-point scale adapted from the Krenning score for Octreoscan [12]: absence of uptake (grade 0), lower than (grade 1), equal to (grade 2) or greater than (grade 3) normal liver tissue or higher than normal spleen or kidney uptake (grade 4). In ^{68}Ga-DOTA-TATE MIP images, each focal, abnormal tracer uptake was recorded by anatomical localization and SUV_{max}. Then lesions seen at different time points on ^{177}Lu-DOTA-TATE were compared to the ^{68}Ga-DOTA-TATE MIP images.

For regional analysis, the body was divided into five sections: head/neck, thorax, liver, abdomen/pelvis and bones. In patients with generalized metastases (more than 15 lesions), only 1 target lesion in each anatomical region was selected for the analysis.

In 115 of 318 lesions, the size of the metastasis (on CT) and the SUV_{max} values were also measured.

Histopathological confirmation was not possible in all of the lesions. Hence, the lesions detected on ^{68}Ga-DOTA-TATE PET/CT were considered to be positive by follow-up for a minimum duration of 6 months with ^{68}Ga-DOTA-TATE PET/CT, CT, MRI, ^{18}F-fluorodeoxyglucose (FDG) PET/CT, ultrasound or biochemical markers.

Statistical analysis

Data were defined as mean ± SD or total number (%). Sensitivity, positive predictive value and accuracy were calculated for detection of lesions on ^{68}Ga-DOTA-TATE and ^{177}Lu-DOTA-TATE studies. Group comparisons between ^{68}Ga-DOTA-TATE and ^{177}Lu-DOTA-TATE were performed using an independent sample *t* test. Spearman's correlation was applied for correlations between the different data. Separate analysis was made for concordant (^{177}Lu-DOTA-TATE and ^{68}Ga-DOTA-TATE positive) and discordant lesions (^{177}Lu-DOTA-TATE negative ^{68}Ga-DOTA-TATE positive or ^{177}Lu-DOTA-TATE positive ^{68}Ga-DOTA-TATE negative). The Statistical Package for the Social Sciences 15 (SPSS 15) statistical software system (SPSS® Inc., Chicago, IL, USA) was used for the calculations. A p value <0.05 was considered as statistically significant.

Results

Interlesional analysis

A total of 318 lesions were evaluated in this study; 280 (88%) lesions were concordant. Among the discordant lesions (12%), 29 (9%) were ^{68}Ga-DOTA-TATE positive and ^{177}Lu-DOTA-TATE negative and 9 (3%) were ^{68}Ga-DOTA-TATE negative and ^{177}Lu-DOTA-TATE positive.

The sensitivity, positive predictive value and accuracy for the detection of NET metastases for ^{177}Lu-DOTA-TATE as compared to ^{68}Ga-DOTA-TATE were 91, 97 and 88%, respectively.

Significantly more lesions (Fig. 1) were seen on the delayed (72 h) ^{177}Lu-DOTA-TATE images (91%) as compared to the immediate (30 min) (68%) or early (2 h) scans (82%) [p= 0.000 and odds ratio 1.4 (95% confidence interval 1.2–1.6)].

Among the concordant lesions, the highest agreement was observed for bone metastases (97%) followed by liver (88%), abdomen (83%) and lesions in the thorax (80%). The lowest concordance was found for metastases in the head/neck region (75%) (Fig. 2).

The analysis of tumour size showed that concordant lesions (n=77; mean size 3.8 cm) were significantly larger than discordant lesions (n=38; mean size 1.6 cm) (p<0.05)

The analysis of SUV_{max} showed no significant difference between concordant and discordant lesions.

There was a significant correlation between the 72-h ^{177}Lu-DOTA-TATE visual intensity scores and the ^{68}Ga-DOTA-TATE SUV_{max} for lesions in the thorax, abdomen/pelvis and skeletal system (p<0.05). This correlation was not shown for liver lesions. However, concordant liver lesions with a ^{177}Lu-DOTA-TATE score from 1 to 3 in the 72-h ^{177}Lu-DOTA-TATE scan had a lower SUV_{max} (n=23; mean 10.9) than those metastases with a ^{177}Lu-DOTA-TATE score of 4 (n=97; mean SUV_{max} 18) (p<0.05) (Tables 2 and 3).

Among the discordant lesions, 29 of 318 were ^{68}Ga-DOTA-TATE positive and ^{177}Lu-DOTA-TATE negative. Among these lesions, ten (34%) were located in the liver, eight (28%) in the abdomen/pelvis region, six (21%) in the thorax, three (10%) in the bone and two (7%) in the head/neck region. Fifteen (52%) of the ^{68}Ga-DOTA-TATE positive and ^{177}Lu-DOTA-TATE negative lesions were lymph nodes, ten (34%) liver metastases, three (10%) bone metastases and one pleural metastasis.

There were 9 of 318 lesions which were ^{68}Ga-DOTA-TATE negative and ^{177}Lu-DOTA-TATE positive (this pattern was observed in 5 patients overall). Seven lesions (in three patients) were found in the liver (Fig. 3), one was located in the pelvis and one in the neck.

In this study, all lesions which were detected by either imaging modality were located in parts of the body covered

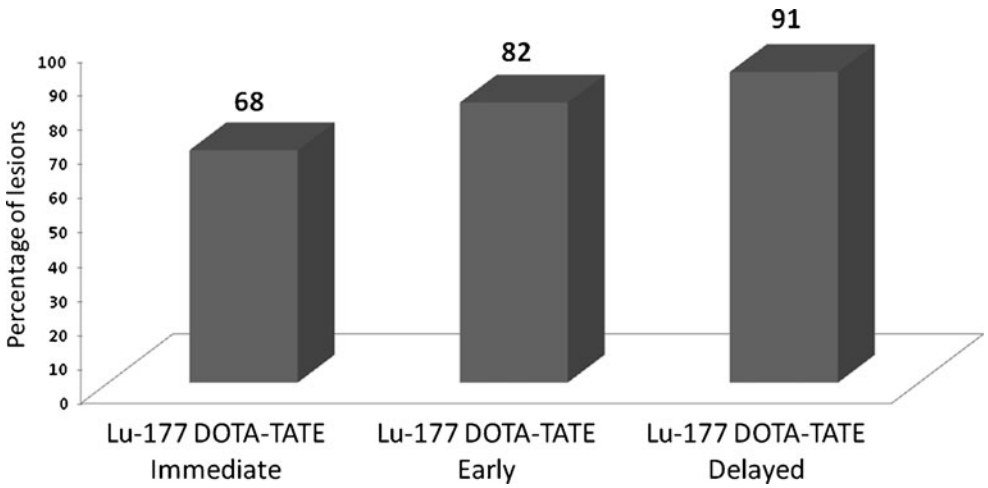

Fig. 1 Comparison of the sensitivity of ^{177}Lu-DOTA-TATE planar images at 0.5 (immediate), 2 (early) and 72 h (delayed) for the detection of the primary tumour and sites of metastasis of NET

by ^{68}Ga-DOTA-TATE PET/CT (brain to mid-thigh). The ^{177}Lu-DOTA-TATE scan did not reveal any additional lesion in the distal extremities.

Patient-based analysis

A total of 14 patients had 5 or less metastases, 20 had 6–8 and 10 had more than 10 metastases. In all patients, both imaging techniques were positive for at least one lesion; however, in six patients, ^{68}Ga-DOTA-TATE showed malignant involvement in regions that were negative for ^{177}Lu-DOTA-TATE (in two patients ^{68}Ga-DOTA-TATE revealed liver metastases, in another two patients thoracic lesions and in two patients abdominal spread). In one patient, ^{177}Lu-DOTA-TATE showed liver involvement that was not detected on ^{68}Ga-DOTA-TATE.

Discussion

^{68}Ga-DOTA-TATE is a somatostatin receptor subtype 2 ligand which is being increasingly used for somatostatin receptor PET/CT imaging of NET. It offers very good target to non-target imaging properties that make it an ideal PET radiotracer [7, 20]. ^{68}Ga-DOTA-TATE PET/CT has proven to be an accurate method for detecting primary tumours and metastases, in particular for well-differentiated NET [21, 22]. The higher resolution of PET/CT systems with the ability of acquiring tomographic images, directly correlated to anatomy, results in significantly higher sensitivity for lesion detection when compared to ^{111}In- or ^{99m}Tc-labelled somatostatin analogues [23].

In patients with inoperable or metastatic well-differentiated NET, PRRT with ^{177}Lu-DOTA-TATE has shown very

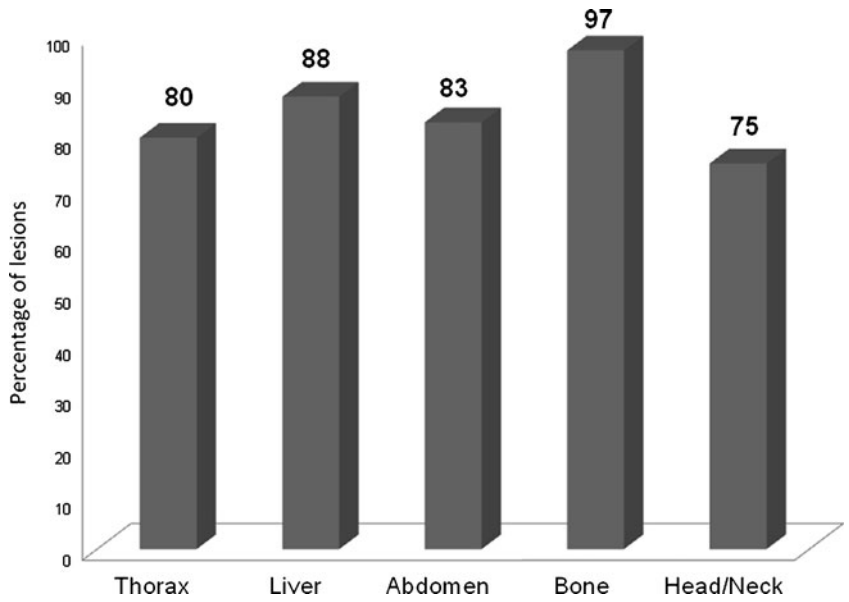

Fig. 2 Sensitivity of the delayed ^{177}Lu-DOTA-TATE planar images for the detection of the primary tumour and sites of metastasis of NET depending on the anatomical region

Table 2 Comparison between SUV_{max} on ^{68}Ga-DOTA-TATE and visual score on ^{177}Lu-DOTA-TATE

	Mean ^{68}Ga-DOTA-TATE SUV_{max}	Mean ^{177}Lu-DOTA-TATE visual score
Liver lesions	15.35±8.82	3.46±1.11
Bone lesions	9.89±7.99	2.54±1.26
Lymph node lesions	9.09±6.78	1.49±1.29

encouraging results [14, 18] with only minor side effects and good overall median duration of survival [13]. ^{177}Lu, apart from intermediate beta energy (suitable for PRRT), also emits gammas suitable for scintigraphy and subsequent dosimetry. As part of the routine practise, in the Department of Nuclear Medicine/PET Centre, Bad Berka, Germany, all of the patients undergoing PRRT with ^{177}Lu-DOTA-TATE are scanned in order to perform dosimetric calculations. Whole-body planar images are acquired and a standard with a known aliquot of the injected dose is also counted. In our study, we have retrospectively compared the dosimetric ^{177}Lu-DOTA-TATE whole-body planar scans with the pre-therapeutic ^{68}Ga-DOTA-TATE scans performed for diagnostic purposes. This is why the ^{177}Lu-DOTA-TATE images included in this study are performed with a therapeutic dose of radioligand. As the ^{177}Lu-DOTA-TATE images were performed for dosimetric purposes, no complementary projections or tomographic images were acquired.

As the aim of the study is to report to what extent lesions in NET detected on ^{68}Ga-DOTA-TATE can also be identified on dosimetric ^{177}Lu-DOTA-TATE scans under therapeutic conditions, data related to adverse reactions after the injection of the ^{177}Lu-DOTA-TATE, side effects or therapeutic outcome of the PRRT are beyond the purpose of the study and are not reported.

In the present study, the ^{177}Lu-DOTA-TATE planar dosimetry scan proved to be an accurate method for the detection of NET metastases with a sensitivity and positive predictive value of 91 and 97% as compared to ^{68}Ga-DOTA-TATE and a lesion concordance rate between the two modalities of 88%. However, it failed to pick up 9% of lesions seen on ^{68}Ga-DOTA-TATE PET/CT.

The highest concordance rate was found for the delayed ^{177}Lu-DOTA-TATE scans. This observation may be related to the kinetics of ^{177}Lu-DOTA-TATE with progressive continuous accumulation in NET metastases and decreasing background activity, which results in a better lesion to background ratio (Figs. 4 and Fig. 5). This was especially evident for bone metastases where physiological uptake in normal bone tissue is very low, providing a very good target to non-target ratio (Fig. 6).

The remaining "discordant group" (12%) could be classified into two categories:

First, ^{68}Ga-DOTA-TATE positive/^{177}Lu-DOTA-TATE negative: Most of the lesions missed by ^{177}Lu-DOTA-TATE in this group were found in the liver and in the abdomen/pelvis region and were lymph nodes. The most probable explanation for these findings is that, in these regions, there is a high background activity due to physiological elimination of the radiotracer through the bowel, as well as organ superposition, which result in a lower sensitivity in planar images, especially in small structures like lymph nodes. This assumption is supported by the fact that concordant lesions were significantly larger than discordant lesions (Table 4). In addition, the ^{68}Ga-DOTA-TATE studies provide a higher spatial resolution than the ^{177}Lu-DOTA-TATE planar images [21–23]. Therefore, dosimetry calculations based on planar ^{177}Lu-DOTA-TATE scans will miss some of the lesions. This could possibly be avoided by three-dimensional dosimetry using single photon emission computed tomography (SPECT)/CT. This hybrid modality has proven to increase the diagnostic accuracy [24, 25] and its use for dosimetry has already been suggested [26, 27]; however, SPECT/CT needs to prove its superiority for dosimetric purposes.

Another possible explanation for this discrepancy could be that the tumour cell accumulation capacity under therapeutic conditions may be altered due to the biological

Table 3 Mean SUV_{max} according to localization of metastases and respective visual score on ^{177}Lu-DOTA-TATE at 72 h

	Liver		Lymph nodes		Bone	
^{177}Lu-DOTA-TATE visual score	Number of lesions	Mean SUV_{max}	Number of lesions	Mean SUV_{max}	Number of lesions	Mean SUV_{max}
0	10	10.90±2.50	16	5.96±4.39	4	2.55±1.06
1	1	8.00	20	5.79±2.97	19	3.97±1.84
2	4	11.43±1.35	11	9.97±3.12	17	6.61±2.84
3	22	8.93±6.02	7	12.60±4.99	20	10.41±5.57
4	100	17.44±9.05	7	20.80±10.19	27	16.82±9.51

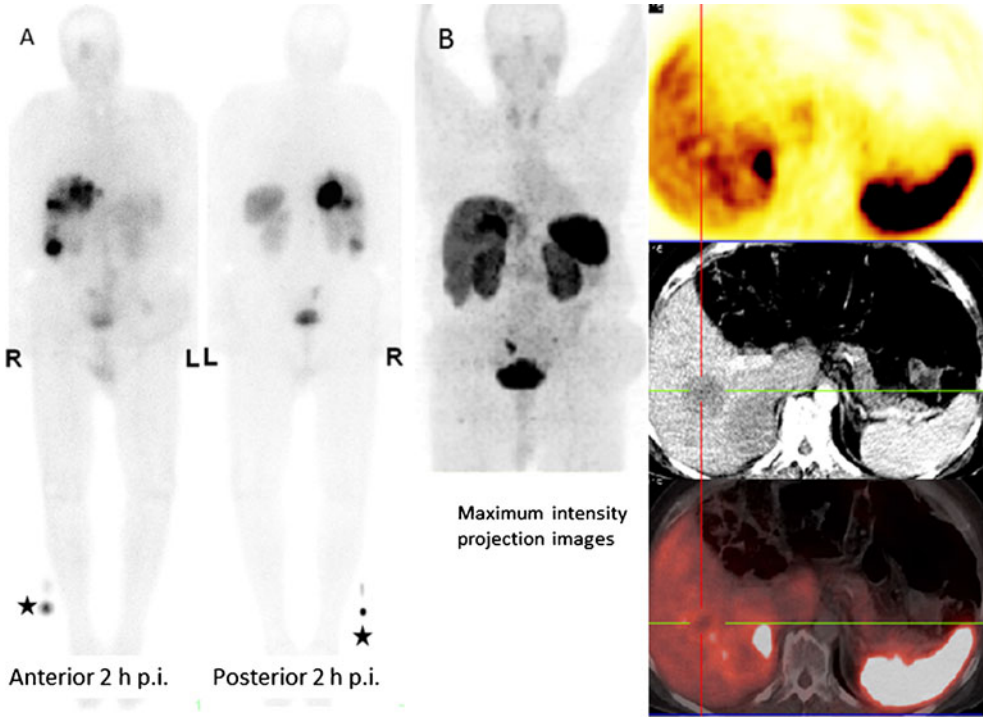

Fig. 3 Example of discordant lesions. **a** Liver metastases were only seen on ^{177}Lu-DOTA-TATE planar scintigraphy performed 2 h after injection in a patient with NET. **b** ^{68}Ga-DOTA-TATE PET/CT shows a hypodense lesion on the CT scan which reveals a donut pattern (MIP images, transverse PET, transverse CT and transverse fused PET/CT)

effects of the radiation from the ^{177}Lu-DOTA-TATE. In our opinion, this explanation is not very probable because the radiobiological effects are more likely to be expected in the delayed scans and especially in the lesions with a very high uptake. However, the delayed scans showed more lesions when compared to the immediate or early scans and the lesions with very high uptake are more likely to be visible in the scans.

Second, ^{68}Ga-DOTA-TATE negative/^{177}Lu-DOTA-TATE positive: This pattern was present for nine lesions in five patients and mainly observed in liver

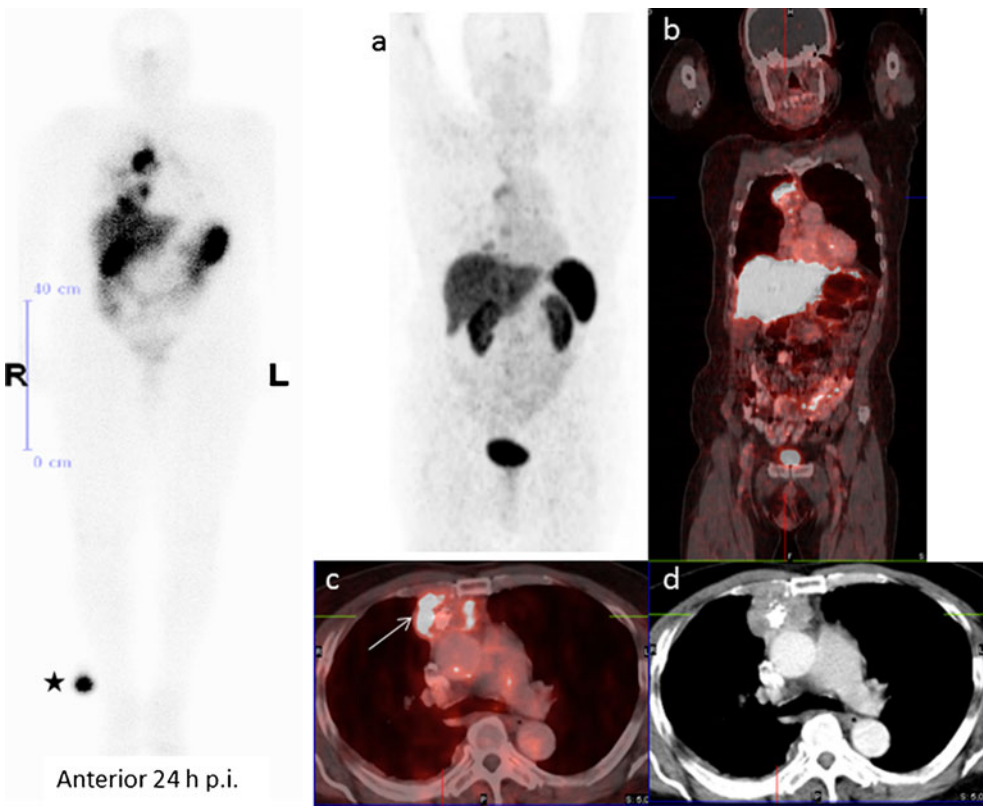

Fig. 4 Example of concordant lesions. ^{177}Lu-DOTA-TATE planar dosimetry scan anterior projection, performed 24 h after injection (*left*) in a patient with NET, demonstrates multiple metastases in the mediastinum. The tumour uptake in the lesions is higher than normal liver (grade 4). ^{68}Ga-DOTA-TATE (*right*) (**a** MIP images, **b** coronal fused PET/CT, **c** transverse fused PET/CT and **d** CT) shows the same lesions (*arrow*) but with less intense uptake than on the ^{177}Lu-DOTA-TATE scan. Activity standard for dosimetric purposes (*star*)

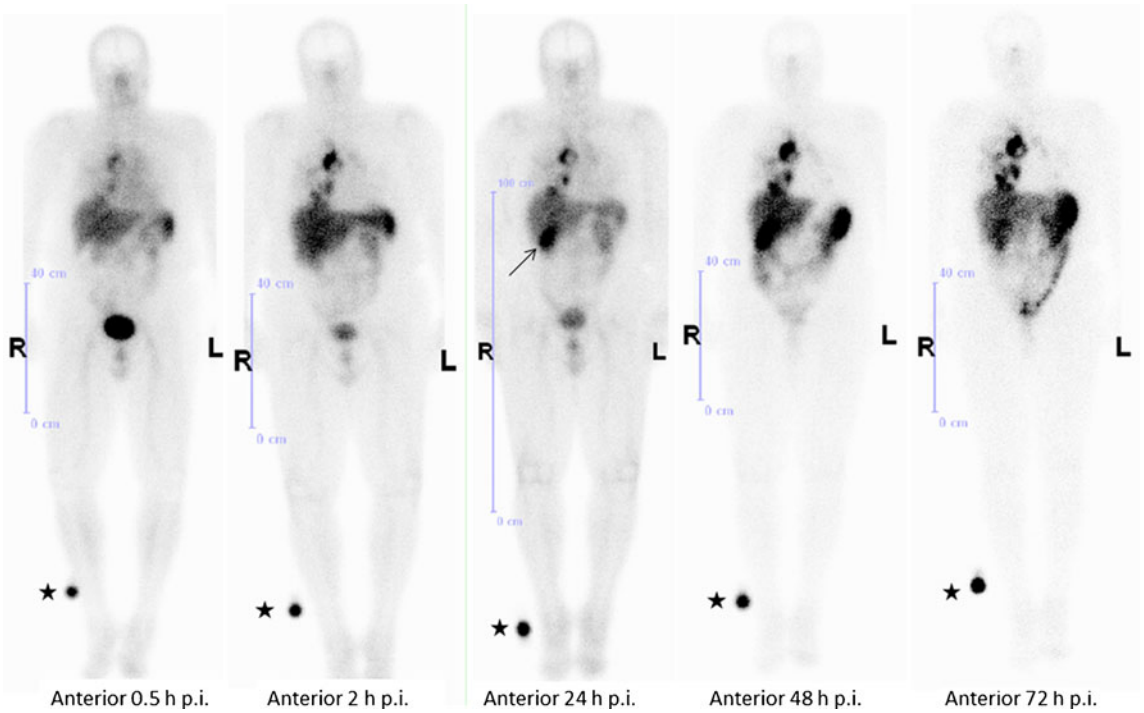

Fig. 5 Sequential ^{177}Lu-DOTA-TATE anterior planar scans for the same patient as in Fig. 4. The abnormal mediastinal uptake is higher in the delayed scan. Observe the decreasing background activity over time. Notice the activity in the gall bladder in the 24-h scan (*arrow*) and the subsequent increasing bowel activity due to the physiological elimination in the following images. Activity standard for dosimetric purposes (*star*)

lesions in a few patients (seven lesions in three patients). Two of these ^{177}Lu-DOTA-TATE positive liver lesions (in one patient) were detected 6 months later, also by ^{68}Ga-DOTA-TATE, performed after ^{177}Lu-DOTA-TATE therapy. The explanation for the disparity between the imaging procedures in these lesions may concern the somatostatin analogue compound labelled to the radioisotope (in our study the same compound with different concentrations); the physical and chemical characteristics of the two different radioisotopes (^{68}Ga and ^{177}Lu) as well as the dose injected; and the histological characteristics of the lesions (in our study a wide and heterogeneous group) as well as the intra-individual variations.

Although ^{177}Lu-DOTA-TATE and ^{68}Ga-DOTA-TATE had been performed with the same somatostatin analogue (DOTA-TATE), a possible explanation for the difference in radiotracer uptake could be the higher amount of peptide used for ^{177}Lu-DOTA-TATE therapy. Velikyan et al. studied nine patients with gastroenteropancreatic NET. Six of them underwent three sequential PET/CT examinations with

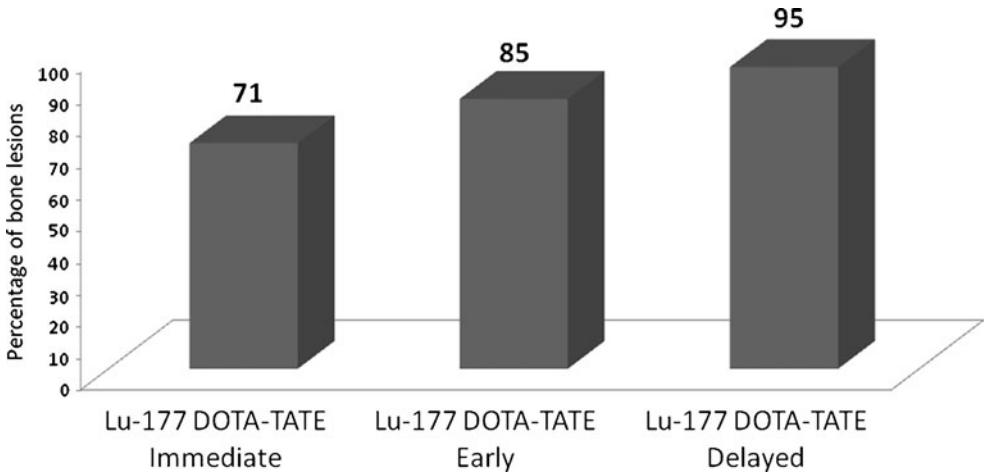

Fig. 6 Comparison of the sensitivity of ^{177}Lu-DOTA-TATE planar images at 0.5 (immediate), 2 (early) and 72 h (delayed) for the detection of bone metastases of NET

Table 4 Concordant and discordant lesions according to SUV_{max} and size

	SUV_{max}		Size (mm)	
	Mean	Median	Mean	Median
All lesions (n=318)	12.99	11.35		
Concordant lesions (n=77)	10.91	10.90	30.84	25.00
Discordant lesions (n=29)	6.70	5.50	15.69	15.00

intravenous injections of ^{68}Ga-DOTATOC (specific radioactivity: 25–50 MBq/nmol) preceded by 0.50 and 250 or 500 μg (0, 49, 245 and 491 nmol, respectively) octreotide, which was administered 10 min before the tracer injection. The tracer accumulation in the tumours varied and depended on the total amount of the peptide administered. Compared to the baseline study (0 μg of octreotide), there was first an increase (50 μg of octreotide) and then a decrease (250 or 500 μg of octreotide) in the tumour uptake. An exception was one patient showing a continuously increasing tumour uptake. Interestingly, a significant mass effect was also found on the tracer binding in non–tumoural tissues [28].

Discordances in the biodistribution of any molecule when labelled with different radionuclides for diagnostic or therapeutic purposes are known. Small structural modifications, chelator substitution or metal replacement were shown to considerably affect the binding affinity [3, 18, 29–31]. A possible explanation for the image discrepancies could be related to the different characteristics of the two chemical elements (ionic radii, radiometal effects).

Another probable explanation could be the diverse radiotracer kinetics that depend on the lesion type (cystic or solid) and the differences in the biological half-life of the two radiotracers [3]. It is known that ^{177}Lu-DOTA-TATE has a higher residence time in tumours when compared with other ^{177}Lu-labelled peptides [32]. Possibly, in some type of (cystic) lesions, the uptake is very slow and the target to non-target ratio is only high enough to detect such a lesion long after the intravenous injection ("filling in effect"). It can be specifically observed in the liver, where the physiological uptake is relatively high (as compared for example to bone). This might explain why a lesion is only detected by a radiotracer with a long half-life like ^{177}Lu-DOTA-TATE (160 h) and not by ^{68}Ga-DOTA-TATE (68 min). Mirzaei et al. had reported additional lesions detected in therapeutic scans with ^{177}Lu-DOTA-TATE when compared to the diagnostic scan performed with ^{99m}Tc-EDDA/HYNIC-TOC in the same patients. In their study, a diagnostic scan was performed 2–3 h after the radiotracer injection while the post-therapeutic scan was performed 24 and 72 h post-injection [26].

It is, therefore, of great interest to perform PET/CT studies in these patients with long-lived PET isotopes like ^{44}Sc or ^{86}Y, especially in pre-therapeutic use. Jamar et al. [19] and Helisch et al. [29] described the use of ^{86}Y-DOTATOC before the therapeutic use of ^{90}Y. However, the limited availability of these isotopes and their decay mode with additional high-energy gamma rays, requiring elaborate correction algorithms, preclude their routine clinical use. Nevertheless, in this case, the use of long-lived PET radiotracers enables a direct comparison in the same modality, avoiding the comparison between planar and tomographic images.

Of the other two lesions, one was found in the pelvis (possibly corresponding to an intrauterine lesion DD myoma) and one was found in the head/neck region. Unfortunately, there is no available histological confirmation for this latter lesion, but it was confirmed as an enlarging metastasis in follow-up studies.

Limitations of the study

The study included a rather heterogeneous population of different NET subtypes. This has to be balanced against a reasonably sized patient population, especially with regard to the fact that these tumours are relatively rare. The histopathological confirmation was not ethically possible in patients with discordant lesions. However, each patient was widely studied with close clinical monitoring and follow-up studies for a minimum duration of 6 months with ^{68}Ga-DOTA-TATE PET/CT, CT, MRI, ^{18}F-FDG PET/CT, ultrasound or biochemical markers.

Conclusion

^{177}Lu-DOTA-TATE planar dosimetry scans exhibit a very good sensitivity for the detection of metastases in NET, showing good concordance with ^{68}Ga-DOTA-TATE. The highest concordance rate was found for the delayed ^{177}Lu-DOTA-TATE (72 h) images, these being the most suitable images for dosimetric calculations. However, ^{177}Lu-DOTA-TATE failed to pick up 9% of lesions seen on ^{68}Ga-DOTA-TATE PET/CT. Most of the missed lesions were small lesions located in the liver and in the abdominal/pelvis region. The most probable explanation for this discrepancy is the better tomographic resolution of ^{68}Ga-DOTA-TATE. Dosimetry calculations based only on planar ^{177}Lu-DOTA-TATE scans will certainly miss some of the lesions, giving an erroneous result. This could possibly be avoided by three-dimensional dosimetry using SPECT/CT. A few lesions were only detected on ^{177}Lu-DOTA-TATE scans. Higher amounts of peptides used in ^{177}Lu-DOTA-TATE scans, different radiotracer kinetics, depending on the lesion type, or differences in the chemical or physical radionuclide characteristics might explain this discrepancy.

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Authors' contributions Each author has contributed significantly to the submitted work. Aurora Sainz-Esteban contributed to the conception and design of the study, acquired, analysed and interpreted the data and wrote the manuscript. Vikas Prasad contributed to the conception and design of the study, performed the PET/CT and the dosimetry studies, analysed the data and critically revised and approved the final manuscript. Christiane Schuchardt and Carolin Zachert performed the dosimetry studies and critically read the manuscript. José Manuel Carril critically revised and approved the final manuscript. Richard Paul Baum conceived the study, performed the PET/CT and dosimetry studies and critically revised and approved the final manuscript.

Conflicts of interest None.

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