Eur Radiol (2016) 26:900–909
DOI 10.1007/s00330-015-3882-1

NUCLEAR MEDICINE

Comparison of diagnostic accuracy of ^{111}In-pentetreotide SPECT and ^{68}Ga-DOTATOC PET/CT: A lesion-by-lesion analysis in patients with metastatic neuroendocrine tumours

S. Van Binnebeek[1] · B. Vanbilloen[1] · K. Baete[1] · C. Terwinghe[1] · M. Koole[1] · F. M. Mottaghy[2,3] · P. M. Clement[4] · L. Mortelmans[1] · K. Bogaerts[5] · K. Haustermans[6] · K. Nackaerts[7] · E. Van Cutsem[8] · C. Verslype[8] · A. Verbruggen[9] · C. M. Deroose[1,10]

Received: 15 October 2014 / Revised: 4 May 2015 / Accepted: 8 June 2015 / Published online: 12 July 2015

Abstract

Objectives To compare the diagnostic accuracy of ^{111}In-pentetreotide-scintigraphy with ^{68}Ga-DOTATOC-positron emission tomography (PET)/computed tomography (CT) in patients with metastatic-neuroendocrine tumour (NET) scheduled for peptide receptor radionuclide therapy (PRRT). Incremental lesions (ILs) were defined as lesions observed on only one modality.

Methods Fifty-three metastatic-NET-patients underwent ^{111}In-pentetreotide-scintigraphy (24 h post-injection; planar+single-photon emission CT (SPECT) abdomen) and whole-body ^{68}Ga-DOTATOC-PET/CT. SPECT and PET were compared in a lesion-by-lesion and organ-by-organ analysis, determining the total lesions and ILs for both modalities.

Results Significantly more lesions were detected on ^{68}Ga-DOTATOC-PET/CT versus ^{111}In-pentetreotide-scintigraphy. More specifically, we observed 1,098 lesions on PET/CT (range: 1–105; median: 15) versus 660 on SPECT (range: 0–73, median: 9) ($p<0.0001$), with 439 PET-ILs (42/53 patients) and one SPECT-IL (1/53 patients). The sensitivity for PET/CT was 99.9 % (95 % CI, 99.3–100.0), for SPECT 60.0 % (95 % CI, 48.5–70.2). The organ-by-organ analysis showed that the PET-ILs were most frequently visualized in liver and skeleton.

Conclusion Ga-DOTATOC-PET/CT is superior for the detection of NET-metastases compared to ^{111}In-pentetreotide SPECT.

Key Points

- *Somatostatin receptor PET is superior to SPECT in detecting NET metastases*
- *PET is the scintigraphic method for accurate depiction of NET tumour burden*
- *The sensitivity of PET is twofold higher than the sensitivity of SPECT*

Keywords ^{68}Ga-DOTATOC · ^{111}In-pentetreotide · SPECT · PRRT · Neuroendocrine tumour

✉ C. M. Deroose
christophe.deroose@uzleuven.be

1 Nuclear Medicine, University Hospitals Leuven and Department of Imaging and Pathology, KU Leuven, Leuven, Belgium

2 Department of Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

3 Department of Nuclear Medicine, University Hospital Aachen, Aachen, Germany

4 Medical Oncology, University Hospitals Leuven and Laboratory of Experimental Oncology, KU Leuven, Leuven, Belgium

5 Department of Public Health and Primary Care (I-BioStat), KU Leuven and UHasselt, Leuven, Belgium

6 Radiation Oncology, University Hospitals Leuven and Department of Oncology, KU Leuven, Leuven, Belgium

7 Pulmonology, University Hospitals Leuven, Leuven, Belgium

8 Division of Digestive Oncology, University Hospitals Leuven and Department of Oncology, KU Leuven, Leuven, Belgium

9 Laboratory for Radiopharmacy, KU Leuven, Leuven, Belgium

10 Nuclear Medicine, University Hospitals Leuven, Leuven, Belgium

Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours originating from neuroendocrine cells within a number of different organs [1]. Many NETs overexpress specific G-protein coupled transmembrane receptors on their cell surface, of which the somatostatin receptor (SSR) is the most abundant and best studied. To date, five receptor subtypes

have been characterized [2], all of which are expressed with different frequencies in gastroenteronpancreatic (GEP)-NETs. SSR_2 and SSR_5, for example, are expressed at a high densitivity in 70 %–100 % of GEP-NETs [3]. These SSRs are used as a target for diagnostic and therapeutic radiopharmaceuticals. Planar and single-photon emission computed tomography (SPECT) imaging using ^{111}In-diethylenetriaminepentaacetic acid (DTPA)-octreotide (^{111}In-pentetreotide), a SSR_2-specific tracer [2], is an established imaging modality for the diagnosis of SSR-positive NETs [4]. Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues (SSAs) is an established treatment in Europe in the management of patients with inoperable or metastatic neuroendocrine tumors [5, 6]. Recently, gallium-68-based radiopharmaceuticals such as ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE or ^{68}Ga-[DOTA,1-Nal^3]-octreotide (DOTANOC) showed promising results for the diagnosis of NETs [7–11], with a higher detection rate compared to ^{111}In-pentetreotide SPECT in a limited series of publications [12–15]. Our aim was to confirm the hypothesis that ^{68}Ga-DOTATOC PET/CT has a higher lesion detection rate than ^{111}In-pentetreotide scintigraphy with SPECT-imaging, thereby comparing SPECT-images with the PET/CT where only the field of view of the SPECT was taken into account on the PET/CT image. We specifically looked for incremental lesions (ILs), defined as lesions only observed on one modality even after extensive retrospective evaluation of the other modality. Furthermore, we evaluated and compared the different tumour locations to determine the organs in which metastases would be missed with the highest frequency.

Materials and methods

Study population

The study group consisted of 53 patients with metastatic NET, enrolled in a prospective phase II monocentric trial with ^{90}Y-DOTATOC. Thirty-nine primary tumours were from gastroenteropancreatic origin, four from the lung, two were Merckel cell carcinomas and two were from other primary locations (breast and kidney), with the remaining six from unknown origin. All were histologically confirmed. All patients (30 women and 23 men, all from Caucasian origin; age range 31–80 y, mean 59 ± 12 y) underwent an ^{111}In-pentetreotide scintigraphy (injected activity 185MBq) with SPECT, used for dosimetry prior to ^{90}Y-DOTATOC-PRRT, and a ^{68}Ga-DOTATOC PET/CT (injected activity 185MBq). Clinical and tumour characteristics as well as imaging details are shown in Table 1.

This prospective trial was approved by the Ethics Commission of the University Hospitals Leuven (S51403), and all patients gave written informed consent, in particular consenting to PRRT as well as to both scintigraphies.

Radiopharmaceuticals

^{68}Ga-DOTATOC

^{68}Ga-DOTATOC ($T_{1/2}$ = 68min) is a complex of gallium-68 with DOTA-(Tyr^3)-octreotide [(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra-acetic acid)-*D*-Phe-Cys-Tyr-*D*-Trp-Lys-Thr-Cys-Thr-ol] (DOTATOC). It has been used in several hundreds of patients in many centres throughout Europe since its introduction in 2001 [7]. It was prepared by heating a solution of gallium-68 chloride (400–800 MBq) at pH 4–4.4 with 33 μg GMP-produced DOTATOC (Bachem, Switzerland) for 8 min at 90°C, adapted from a published method [16]. ^{68}Ga-chloride solution was obtained by elution of a germanium-68/gallium-68 generator (IGG 100-3M ^{68}Ga generator, distributed by Eckert and Ziegler) with diluted HCl-solution followed by purification of the eluate over a Dowex column (Sigma-Aldrich/Fluka, St. Louis, MO, USA) as described previously [16]. All reagents used in the preparation of ^{68}Ga-DOTATOC are of pharmaceutical quality. After the labelling reaction, the reaction mixture was purified over a Sep-Pak C18 column and formulated into an injectable solution. Before administration, the quality of the final solution was analysed according to the European Pharmacopoeia (Ph. Eur.) using a standard procedure, including high pressure liquid chromatography for confirmation of identity of the radioligand and testing of (radio)chemical purity. Tests for sterility, radionuclidic impurities and bacterial endotoxins were performed after use, in accordance with the prescriptions of the Ph. Eur. Several validation preparation runs had proven the compliance of the preparations with these parameters.

^{111}In-pentetreotide

^{111}In-pentetreotide ($T1_{/2}$ = 67.3h) was prepared from a commercially available kit (OctreoScan®, Mallinckrodt Medical B.V., Petten, The Netherlands). The radiolabelling was performed according to the manufacturer's instructions.

Imaging procedures

^{68}Ga-DOTATOC PET/CT

All PET studies were acquired using an integrated Siemens Biograph Hirez 16-slice LSO PET-CT system (Siemens Medical, Erlangen, Germany). Patients receiving therapy with somatostatin analogues, interrupted their analogues 24 h before the PET/CT scan in the case of short-acting SSAs, or 4–6 weeks before the PET/CT scan in the case of long-acting SSAs.

Whole-body (WB) ^{68}Ga-DOTATOC PET/CT images from the head to mid-femur were acquired (seven to nine bed

Table 1 Patient characteristics

No.	Sex	Age at PRRT1(y)	Primary tumour	Metastasis	Grade* – Ki67**	Time between two scans	
1	F	56	Small intestine	Liver; LN; P	G1 – 2 %	2 days	111In before 68Ga
2	F	43	Lung	Liver; bone	G1 – <2 %	2 days	111In before 68Ga
3	F	38	Small intestine	Liver	G1 – <2 %	2 days	111In before 68Ga
4	M	59	Small intestine	Liver, LN	G2 – 4 %	2 days	111In before 68Ga
5	M	63	Colon	Liver, bone, LN, Myocardium, P, ST, Others	G1 – <2 %	2 days	111In before 68Ga
6	F	56	Small intestine	Liver, LN	G2 – 12 %	2 days	111In before 68Ga
7	M	64	Small intestine	Liver, bone, lung, LN,	G1 – 2 %	2 days	111In before 68Ga
8	F	51	CUP	Liver, LN	G2 – 3 %	2 days	111In before 68Ga
9	M	69	Small intestine	Liver, bone, LN, P	G1 – <2 %	2 days	111In before 68Ga
10	F	57	Small intestine	Liver, LN	G2 – <5 %	2 days	111In before 68Ga
11	F	78	CUP	Liver, LN, P	G1 – <2 %	2 days	111In before 68Ga
12	F	67	Breast	Liver, LN, bone	G2 – 10 %	2 days	111In before 68Ga
13	F	66	Small intestine	Liver, LN, P	No result	2 days	111In before 68Ga
14	F	57	Small intestine	Liver, LN, ovaria, P	G2 – 15 %	2 days	111In before 68Ga
15	F	71	Small intestine	Liver, LN	G3 – >20 %	2 days	111In before 68Ga
16	F	80	Small intestine	Ln	G1 – <2 %	2 days	111In before 68Ga
17	F	66	Small intestine	Liver, LN, ovaria, P	G1 – <2 %	2 days	111In before 68Ga
18	F	65	Small intestine	Liver, LN, bone	G1 – 1 to2 %	2 days	111In before 68Ga
19	M	50	Rectum	Liver, LN, bone	G2 – 2.5 %	1 day	111In before 68Ga
20	M	77	Pancreas	Liver, LN, bone	G1 – <2 %	2 days	111In before 68Ga
21	F	73	Small intestine	Liver, LN, bone, ST, P, others	G1 – <2 %	1 month	68Ga before 111In
22	F	77	Merckel cell Ca	Liver, LN, ST, others	G3 – 44 %	7 days	111In before 68Ga
23	M	51	Pancreas	Liver, LN, P	G2 – 5 %	2 days	111In before 68Ga
24	M	75	Pancreas	Liver, LN, bone	G2 – 2 to 5 %	2 days	111In before 68Ga
25	M	58	Lung	Liver, LN, bone	G2 – 10 %	2 days	111In before 68Ga
26	F	59	CUP	Liver, LN, bone, lung,	G2 – 16 %	2 days	111In before 68Ga
27	M	38	Stomach	Liver, LN, bone, lung, ST	G2 – 5 %	2 days	111In before 68Ga
28	F	54	Small intestine	Liver, LN, bone, breast	G2 – <5 %	2 days	111In before 68Ga
29	M	38	Pancreas	Liver, LN, bone	G2 – <5 %	2 days	111In before 68Ga
30	M	55	Small intestine	Liver	G2 – 5 %	2 days	111In before 68Ga
31	F	64	Small intestine	Liver, LN, P	G2 – 5 %	2 days	111In before 68Ga
32	F	68	Small intestine	Liver	G2 – 3 %	2 days	111In before 68Ga
33	M	58	Small intestine	Liver, LN	G1 – <2 %	2 days	111In before 68Ga
34	F	53	Merckel cell Ca	Liver, LN, bone	G3 – 21 %	1 day	111In before 68Ga
35	F	31	CUP	Liver, LN	G2 – 10 %	22 days	111In before 68Ga
36	F	79	Small intestine	Liver, LN	G1 – <2 %	2 days	111In before 68Ga
37	M	67	Small intestine	LN, bone, lung, others	G2 – 5 to 10 %	2 days	111In before 68Ga
38	M	71	Pancreas	Liver, LN	G2 – 2 to 20 %	1 day	111In before 68Ga
39	F	75	Small intestine	Liver, LN, bone, lung, P	G1 – <1 %	2 days	111In before 68Ga
40	M	66	Small intestine	Liver, LN, P	G2 – 5 %	1 day	111In before 68Ga
41	F	43	Lung	Liver, LN, lung, bone, thyroid, others	G2 – 4 %	1 month	68Ga before 111In
42	M	65	Pancreas	Liver, LN, bone	G2 – <5 %	2 days	111In before 68Ga
43	F	72	Lung	Liver, LN	G2 – 9 %	2 days	111In before 68Ga
44	F	65	CUP	Liver, LN, bone	G2 – 10 %	1 day	111In before 68Ga
45	F	65	Small intestine	Liver, LN, bone, P	G1 – <2 %	1 day	111In before 68Ga
46	M	56	Small intestine	Liver, LN, P	G1 – <1 %	18 days	111In before 68Ga
47	M	55	Pancreas	Liver, LN, bone	G3 – 40 %	1 day	111In before 68Ga
48	F	59	Small intestine	Liver, LN, bone, breast	No result	1 day	111In before 68Ga

Table 1 (continued)

No.	Sex	Age at PRRT1(y)	Primary tumour	Metastasis	Grade* – Ki67**	Time between two scans	
49	F	42	Small intestine	Liver, LN, P	G2 – <5 %	2 days	111In before 68Ga
50	M	45	Pancreas	Liver, bone	G2 – 5 %	4 days	68Ga before 111In
51	M	40	CUP	Lung, LN, others	G2 – 10 %	1 month	68Ga before 111In
52	M	62	Small intestine	Liver, LN, skin	G2 – 19 %	2 days	111In before 68Ga
53	M	47	Kidney	Liver, bone	G1 – <1 %	1 day	111In before 68Ga

CUP carcinoma of unknown primary, *LN* lymph nodes, *P* peritoneum, *ST* soft tissue

*According to European Neuroendocrine Tumor Society (eNETs) proposal for grading neuroendocrine tumors

**Ki–67 index was used to determine tumour growth fraction

positions, 4 min scanning time per position) at 30 min after injection of ^{68}Ga-DOTATOC. The contrast-enhanced CT scan, as part of the ^{68}Ga-DOTATOC PET/CT (120 kV, 85 mAS, 5 mm slice thickness), was performed with a 120-mL iodine-containing contrast agent administered intravenously as a bolus (Ultravist, Schering, Mijdrecht, The Netherlands) followed by the ^{68}Ga-DOTATOC PET emission scan covering the same field of view (FOV). PET images were iteratively reconstructed using ordered subsets expectation maximization (OSEM, five iterations, eight subsets) with an in-plane Gaussian post-reconstruction smoothing of 6 mm, both with and without CT-based attenuation correction. The CT data from the ^{68}Ga-DOTATOC PET/CT were used as diagnostic tool, evaluating the head, the thorax, the abdomen and pelvis.

^{111}In-pentetreotide scintigraphy

^{111}In-pentetreotide scintigraphy was performed for dosimetry prior to ^{90}Y-DOTATOC PRRT [17, 18]. At 8 and 24 h post-injection, tomographic views (SPECT) were acquired from the dome of the liver downward, using the aforementioned gamma-camera, with a 128×128 matrix, 20 sec/view and 72 views over 360°. Only SPECT abdomen was performed in every patient since the kidneys, as critical organs during PRRT with ^{90}Y-DOTATOC, had to be in de FOV for dosimetric purposes [19]. On the other hand, most of these study patients had the majority of their tumoral lesions in the abdomen (liver, mesenterium, retroperitoneum, vertebral bone metastases). Due to timing and taking the comfort of the patients into account, we only performed SPECT-images of one region per patient, at 8 h and 24 h after injection.

Clinical and tumour characteristics as well as imaging details are given in Table 1. ^{111}In-pentetreotide scintigraphy with SPECT and ^{68}Ga-DOTATOC PET/CT were obtained in the same week in 47 patients (89 %); in three patients (5.5 %) ^{111}In-pentetreotide scintigraphy was performed 1 month after PET/CT and in three patients (5.5 %) ^{68}Ga-DOTATOC-PET/CT was performed 7, 18 and 22 days after ^{111}In-pentetreotide imaging, respectively.

All 53 patients had an ^{111}In-pentetreotide SPECT of the abdomen.

Image analysis

For the comparative analysis, the non-attenuation corrected (NAC) ^{68}Ga-DOTATOC PET-images and the ^{111}In-pentetreotide SPECT-images at 24 h post-injection were used, except for four patients (patients 35, 41, 46 and 51) where the images at 8 h post-injection were used because the 24-h images were not available. However, in a subset of five patients (data not shown), no difference in the total number of lesions could be seen between these two time points, validating the use of this timepoint. For every patient, the comparison between ^{111}In-pentetreotide SPECT and ^{68}Ga-DOTATOC PET was made, where only the FOV of the SPECT was taken into account on the PET image (=$PET_{FOVSPECT}$) (Fig. 1) and thereby comparing the same part of the body.

One dedicated nuclear medicine physician physician (SVB) assessed the ^{68}Ga-DOTATOC PET/CT and the ^{111}In-pentetreotide WB and SPECT scans, equivocal lesions were decided in consensus with a second senior nuclear medicine physican (CMD). The number of lesions was determined for each patient first on ^{111}In-pentetreotide SPECT and planar images, followed by the ^{68}Ga-DOTATOC images, and then the results were compared; in case of new lesions on scintigraphy or PET, the PET-images or ^{111}In-images, respectively, were re-evaluated, specifically looking for these extra lesions. A tumoral lesion was defined as a focus or an area of increased tracer uptake (with the surrounding tissue as a reference region) which could not be explained by physiological uptake. If there was any doubt about possible physiological uptake or image artefact, the CT-images (as part of the PET/CT) and the corresponding radiology report were consulted.

Histopathology was not available for the vast majority of lesions, which is a known difficulty in studies that look at the presence of metastastic lesions; the standard reference was the maintenance of the lesions on the follow-up scans.

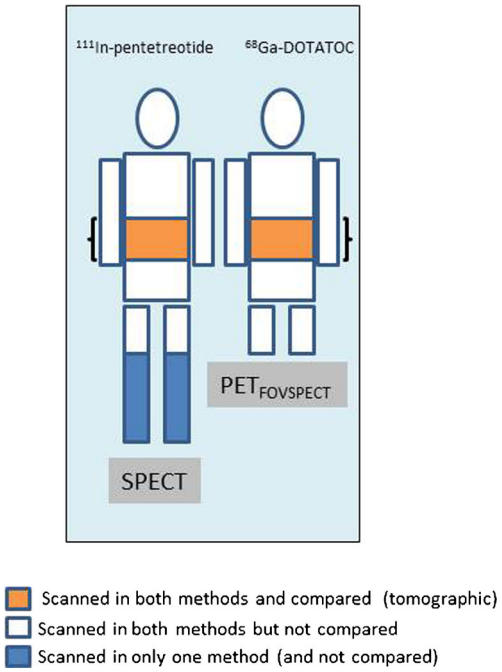

Fig. 1 Comparative analysis of ^{111}In-pentetreotide scintigraphy SPECT and ^{68}Ga-DOTATOC PET/CT and only taking the field of view of the single-photon emission computed tomography (SPECT) into account on the positron emission tomography (PET)/computed tomography (CT) image ($PET_{FOVSPECT}$)

In addition, considering the clinical relevance and to allow a practical comparison, we grouped the metastatic lesions according to four main involved organs: liver, lymph nodes (LN), bone and other locations, based on other articles comparing different tracers in NET patients, where mostly three main regions, classified as 'organs', 'lymph nodes' and 'musculoskeletal system' were defined [13, 14]. Findings on ^{68}Ga-DOTATOC $PET_{FOVSPECT}$ and ^{111}In-pentetreotide SPECT images were compared in a lesion-by-lesion analysis where the total number of lesions as well as the total number of ILs were determined for both modalities. The number of ILs for a modality was expressed as a fraction of the total number of lesions (IL_{ratio}) detected with that modality. Furthermore, an organ-by-organ analysis was made.

PET and SPECT images were evaluated using the HERMES Hybrid Viewer 1.4C (Hermes Medical Solutions, Stockholm, Sweden); ^{111}In-pentetreotide WB-images were scored in MAPS v8.32 (Link Medical, Bramshill, UK).

Statistical analysis

For the descriptive statistics, Excel was used: the absolute and relative number of lesions and incremental lesions is reported using medians, means, maximum/minimum values and interquartile ranges (IQRs).

For the inferential statistics, the comparison between ^{68}Ga-DOTATOC PET and ^{111}In-pentetreotide scintigraphy, tomographically as well as planar and combined, was assessed by a Wilcoxon matched-pairs test (Statistica version 11, StatSoft, Inc., Tulsa, OK, USA). Sensitivity estimates and corresponding 95 % confidence intervals (CIs) were calculated from a generalized estimating equation (GEE) logistic regression model .

Results

^{68}Ga-DOTATOC $PET_{FOVSPECT}$ versus ^{111}In-pentetreotide SPECT

Lesion-based comparison (Table 2)

For ^{111}In-pentetreotide-SPECT, 660 lesions were detected (range: 0–73; median: 9; mean: 12) whereas for ^{68}Ga-DOTATOC $PET_{FOVSPECT}$, a higher total of 1,098 lesions was observed (range: 1–105; median: 15; mean: 21; ($p < 0.0001$). One single IL in one patient out of 53 (2 %) was visualized on ^{111}In-pentetreotide SPECT. In 11 patients (21 %), SPECT and PET images showed the same tumoral lesions

Table 2 Lesion–based comparison of ^{68}Ga–DOTATOC $PET_{FOVSPECT}$ and ^{111}In–pentetreotide SPECT whereby the total number of lesions and incremental lesions, both on positron emission tomography (PET) and single–photon emission computed tomography (SPECT), together with their mean, median and quartile values are shown. The fraction of incremental lesions (ILs) on PET ($IL_{ratio\ PET}$) and SPECT ($IL_{ratio\ SPECT}$) was also calculated, and the mean, median and quartile values are also included

	Total lesions	Mean	Median	$Q_{25\ \%}$	$Q_{75\ \%}$	P–value
^{68}Ga $PET_{FOV\ SPECT}$	1,098	21	15	9	25	$1.7*10^{-5}$
^{111}In SPECT	660	12	9	3	17	
Absolute IL (IL_{PET})	439**	8	5	2	10	
Absolute IL (IL_{SPECT})	1◊					
Fraction IL ($IL_{ratio\ PET}$)	45 %	37 %	34 %	19 %	56 %	
Fraction IL ($IL_{ratio\ spect}$)	0.15 %					

◊ in 1/53 patients; ** in 42/53 patients

and in the remaining 42 out of 53 patients (79 %), 439 ILs (45 % of all PET lesions in patients with ILs) were detected on ^{68}Ga-DOTATOC PET$_{FOVSPECT}$ (Fig. 2A). The sensitivity for PET was 99.9 % (95 % CI, 99.3–100.0) and for SPECT 60.1 % (95 % CI, 48.5–70.2), assuming that all identified lesions are indeed metastatic. When expressed as a fraction of all lesions seen on PET in those 42 patients, the IL$_{ratio}$ on PET$_{FOVSPECT}$ represented on average 37 % (median 34 %; IQR: 19–56 %) (Fig. 2B).

Organ-based comparison (Table 3)

Lesions were, for both ^{68}Ga-DOTATOC PET$_{FOVSPECT}$ and ^{111}In-pentetreotide SPECT, most frequently observed in the liver (PET$_{FOVSPECT}$: n = 593; SPECT: n = 395) and bone (PET$_{FOVSPECT}$: n = 249; SPECT: n = 86) and LN (PET$_{FOVSPECT}$: n = 183; SPECT: n = 129). In every region, besides the skeleton (where only a trend was observed, probably due to the small sample size), significantly more lesions were seen on ^{68}Ga-DOTATOC PET$_{FOVSPECT}$ than on ^{111}In-pentetreotide SPECT (liver: p <0.0001; bone: p = 0.06; LN: p = 0.003; other: p = 0.02). The ILs were also most frequently visualized in the liver (199 lesions or 45 % of all ILs on PET$_{FOVSPECT}$ in 35 patients) and bone (163 lesions or 37 % of all ILs on PET$_{FOVSPECT}$ in 14 patients with a sensitivity of 99.8 % (95 % CI, 99.3–100.0), 100 % and 100 % for PET$_{FOVSPECT}$ and 66.5 % (95 % CI, 57.7–74.3), 34.5 % (95 % CI, 18–55.9) and 70.5 % (95 % CI, 56.1–81.7) for SPECT in liver, bone and LN, respectively, assuming that all identified lesions are indeed metastatic. Figure 3 illustrates ILs on PET in the liver. The only IL on ^{111}In-pentetreotide SPECT was

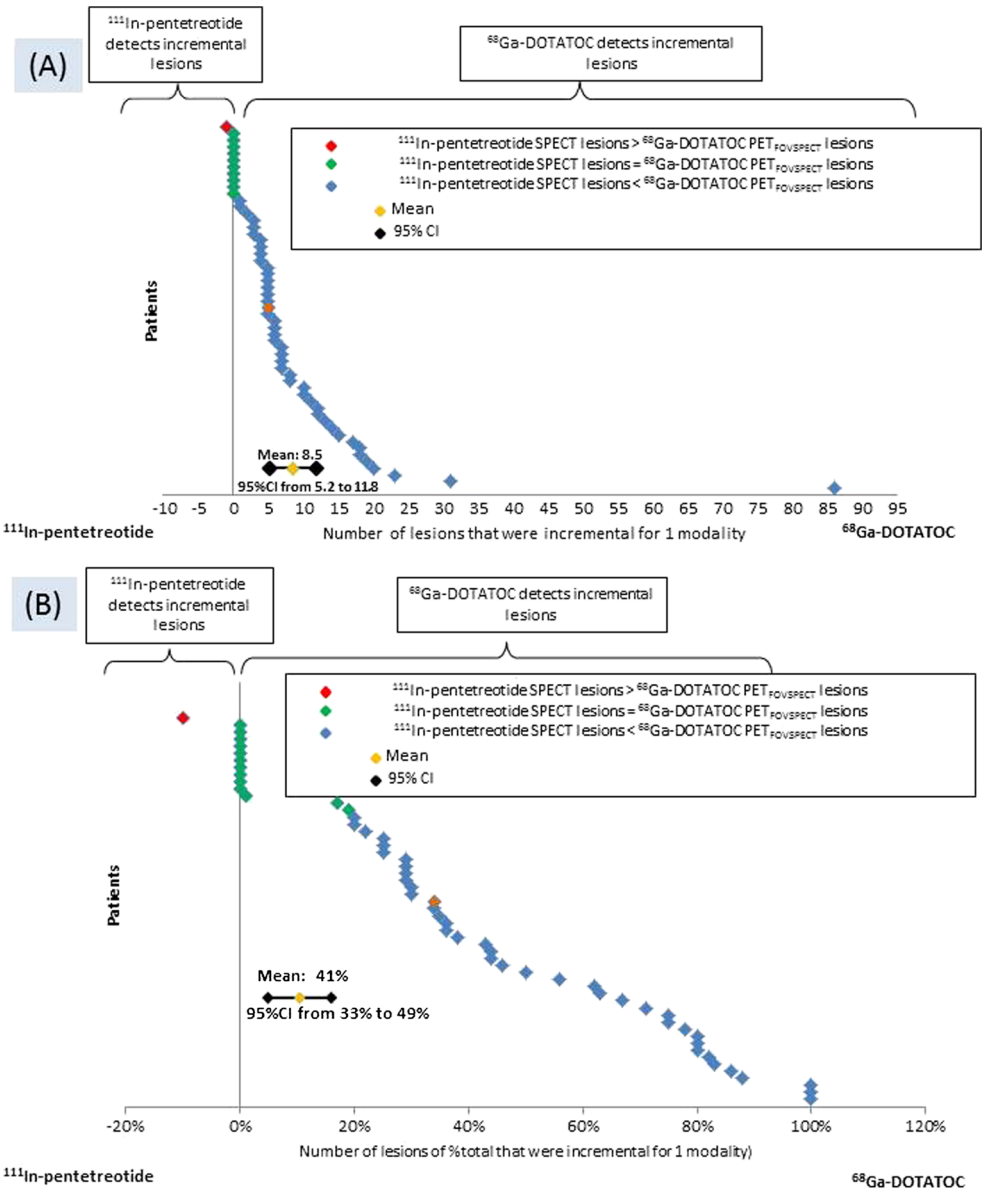

Fig. 2 (**A**) Number of incremental lesions per patient on ^{68}Ga-DOTATOC PET$_{FOVSPECT}$ and ^{111}In-pentetreotide single-photon emission computed tomography (SPECT), and (**B**) relative number of incremental lesions (IL$_{ratio}$) per patient on ^{68}Ga-DOTATOC PET$_{FOVSPECT}$ and ^{111}In-pentetreotide SPECT (% total lesions). The yellow dots represents the patient with the median number of ILs

Table 3 Lesion–based organ–by–organ comparison of ^{68}Ga–DOTATOC $PET_{FOVSPECT}$ and ^{111}In–pentetreotide single–photon emission computed tomography (SPECT) for the liver, the lymph nodes (LN), the bone and other regions (not bone, lymph nodes or liver). The total number of lesions as well as the incremental lesions (ILs) are given; we also added the number of patients in whom ILs were seen

Organ	No. of lesions $PET_{FOVSPECT}$	No. of lesions $SPECT_{total}$	P–value	IL^*_{PET}	IL^*_{SPECT}	No. of patients with IL_{PET} (n=53)	No. of patients with IL_{SPECT} (n=53)
Liver	593	395	$9.7*10^{-5}$	199	1	35 (66 %)	1 (2 %)
LN	183	129	$2.9*10^{-5}$	54	0	14 (26 %)	0
Bone	249	86	$5.5*10^{-2}$	163	0	14 (26 %)	0
Other	73	50	$2.1*10^{-2}$	23	0	9 (17 %)	0
Total	1,098	660	$1.7*10^{-5}$	439	0	42 (79 %)	1 (2 %)

visualized in the liver (Fig. 4), which corresponded to an IL_{ratio} of 13 % in the liver and an IL_{ratio} of 10 % for all lesions seen on SPECT in that patient.

Based on only the SPECT data, another treatment than PRRT could have been chosen for seven out of the 53 patients (13 %): liver-directed therapy in two patients without extra-hepatic metastases on SPECT (#7 and #33), no PRRT in two patients without any ^{111}In-octreotide positive lesion (#2 and #26) and liver surgery in three patients with a clear difference in total number of liver metastases between PET and SPECT (#3, #14 and #41).

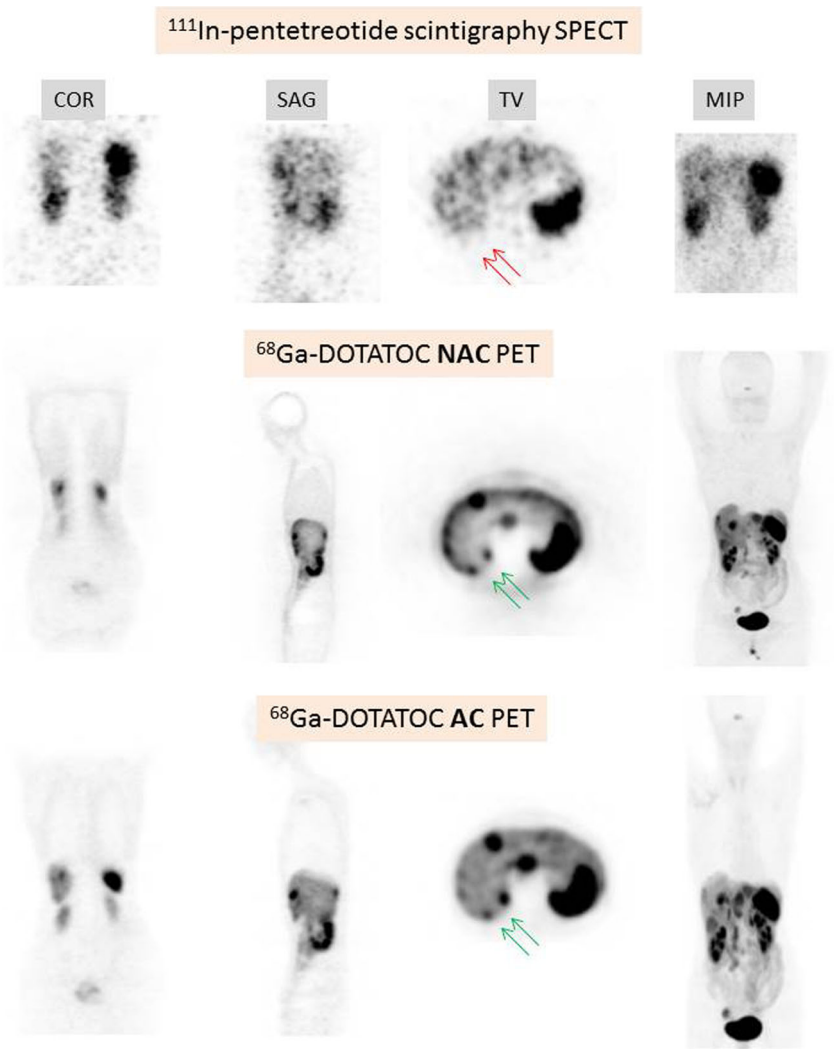

Fig. 3 Patient 7 with two incremental lesions in the liver on ^{68}Ga-DOTATOC $PET_{FOVSPECT}$ without uptake on ^{111}In-pentetreotide single-photon emission computed tomography (SPECT). *COR* coronal, *SAG* sagittal, *TV* transverse, *MIP* maximum intensity projection on ^{111}In-pentetreotide scintigraphy SPECT, ^{68}Ga-DOTATOC NAC and AC PET

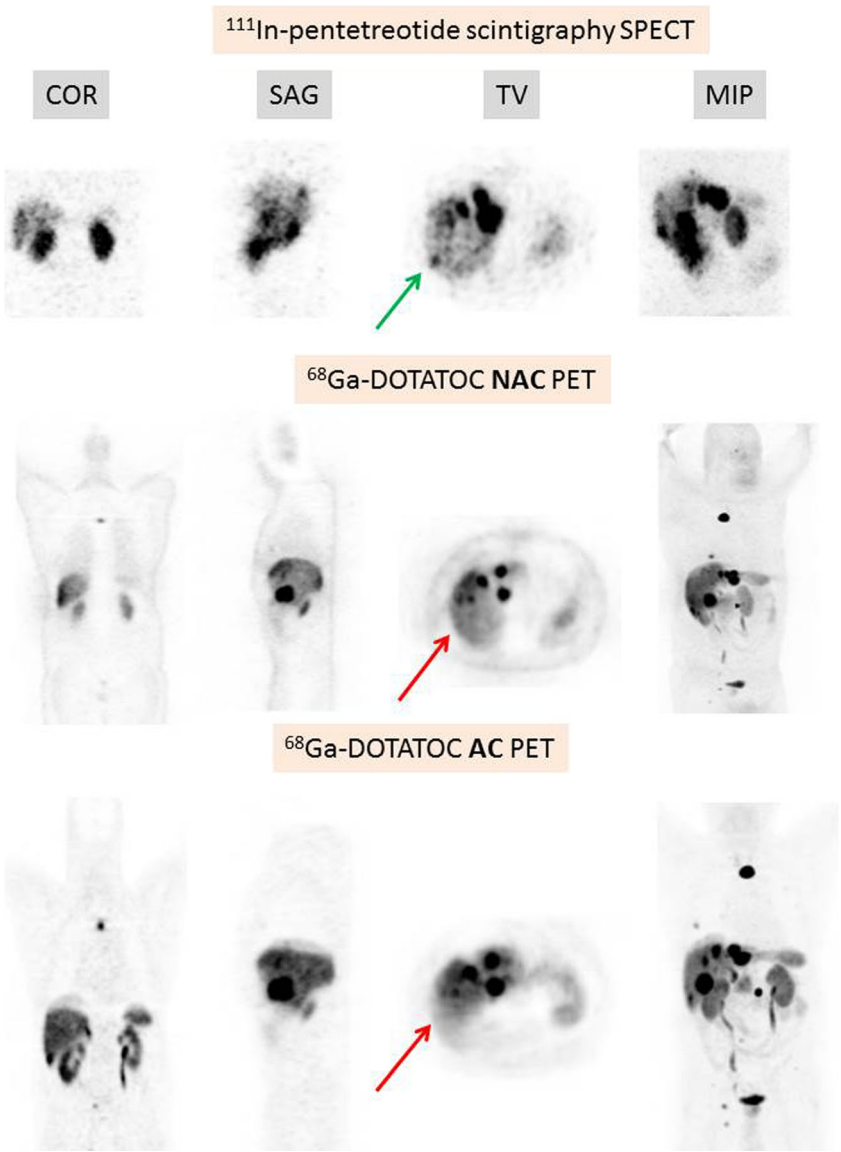

Fig. 4 Single incremental lesion on ^{111}In-pentetreotide SPECT, with location in segment 7 of the liver of patient 20 without uptake on ^{68}Ga-DOTATOC PET. *COR* coronal, *SAG* sagittal, *TV* transverse, *MIP* maximum intensity projection on ^{111}In-pentetreotide scintigraphy SPEC T, ^{68}Ga-DOTATOC NAC and AC PET

Discussion

Our data show the superiority of ^{68}Ga-DOTATOC over ^{111}In-pentetreotide in the detection of NET metastases as PET picked up significantly more tumoral lesions, both on a lesion-based approach and on a region-based analysis, and only taking the FOV of the SPECT into account on the PET/CT image. The ILs on PET correspond to 40 % of all lesions and thus represent a large proportion of the lesions within a single patient.

In two preliminary pilot studies in four [20] and eight [7] study patients, it was observed that the detection rate of ^{68}Ga-DOTATOC PET for NET lesions was higher than that of ^{111}In-DTPA-octreotide. A study by Buchmann et al. [13] on 27 patients demonstrated an increase in lesion detection by ^{68}Ga-DOTATOC PET, most explicitly in the lungs and the skeleton, due to the high amount of small lesions detected on PET, which has a better spatial resolution. In a prospective study by Gabriel et al. in 2007 [12] comparing ^{68}Ga-DOTATOC PET with ^{111}In-DTPA-octreotide SPECT and CT in 84 patients, a higher number of lesions was identified with ^{68}Ga-DOTATOC PET (375) compared to SPECT (302) and CT (295); in particular for the detection of bone metastasis, PET was obviously superior as from the 116 PET-positive lesions, SPECT delineated 84 (72.5 %) and CT only 58 (50 %). Lesions were analysed on both scintigraphic modalities by two different readers, but corresponding studies were compared lesion-by-lesion and in case of discordancy, a third reader was consulted. The CT was analysed separately by a radiologist. No retrospective analysis was performed (which might have led to missing subtle findings) and no incremental lesions were assessed. In Geijer et al. [21], a systematic overview and meta-analysis was performed to determine the diagnostic accuracy of SSR-PET in imaging NET in patients with

known or suspected tumour, expressed as sensitivity and specificity at patient level. The results show that SSR-PET has a high sensitivity (93 %) and specificity (96 %) for evaluation of NETs in the thorax and abdomen. These results are similar to those of a previous meta-analysis [22] which showed a pooled sensitivity of 93 % and specificity of 91 % despite a larger study population (2,105 vs. 567 patients).

Our data show that ^{68}Ga-DOTATOC $PET_{FOVSPECT}$ is better than ^{111}In-DTPA-octreotide SPECT as almost twofold more lesions were detected on $PET_{FOVSPECT}$ (1,098 vs. 660 lesions, respectively), predominantly in the liver, which is explained by the fact that we chose the abdomen as SPECT-region, followed by the bone. This resulted in a sensitivity of 99.9 % (95 % CI, 99.3–100.0) for $PET_{FOVSPECT}$ and 60.1 % (95 % CI, 48.5–70.2) for SPECT. As the SPECT was acquired from the dome of the liver downward in all patients, most of the incremental lesions on $PET_{FOVSPECT}$ were seen in the liver and the only incremental lesion on ^{111}In-pentetreotide SPECT was also localized in the liver. In comparison to SPECT, PET has a two- to threefold higher spatial resolution (15 mm vs. 6 mm), PET has a higher sensitivity for radioactivity (2–4 % vs. 0.02 %), PET is intrinsic tomography and allows more accurate quantification of radioactivity and dynamic imaging. Furthermore, the affinity of ^{68}Ga-DOTATOC in binding SSR_2 (IC_{50} = 2.5±0.5 nM) is tenfold higher than that of ^{111}In-pentetreotide (IC_{50} = 22±3.6 nM) [2] and ^{68}Ga-DOTATOC also binds to SSR_5, while ^{111}In-pentetreotide is a pure SSR_2-agonist [2]. The higher affinity of ^{68}Ga-DOTATOC compared with ^{111}In-pentetreotide and the physical characteristics of gallium-68 result in a lower non-specific radiation exposure of patients and medical staff. In terms of patient friendliness, ^{68}Ga-DOTATOC PET using a 1-hour PET-protocol is more favourable than ^{111}In-pentetreotide scintigraphy with a 2-day conventional protocol; imaging is also faster during PET (18 min for head and body vs. 25 min for 50 cm). In clinical practice, WB SPECT will not routinely be performed in each patient, but planar WB scans are less sensitive than SPECT, as is demonstrated by the fact that the planar images, not taking into account the SPECT-area (total lesions on planar scintigraphy = 150 vs. total lesions on PET without $PET_{FOVSPECT}$ = 660), missed a higher fraction of the total lesions (75 %) than the SPECT images did (40 %) (total number of lesions on SPECT = 660 vs. total lesions on $PET_{FOVSPECT}$ = 1,098) (data not shown). Furthermore, in another economic study, ^{68}Ga-DOTATOC PET/CT was found to be considerably cheaper than ^{111}In-DTPA-octreotide with respect to both material and personnel costs in one study and the use of ^{68}Ga -DOTATOC PET/CT led to considerably fewer additional examinations, which also significantly reduced the total costs [23]. Finally, gallium-68 is a generator radionuclide and is commercially available, but ^{68}Ga-DOTATOC is not yet approved by the US Food and Drug Administration (FDA) nor the European Medicines Agency (EMA), and at this time no kit is commercially available, in contrast to ^{111}In-pentetreotide.

Our comparative study has additional advantages compared to the data that have already been published. First, we investigated a coherent group of patients with metastasized NET, mainly from gastroenteropancreatic origin (74 % of the patient population). Further, the methodology is more optimized and clear. This study has the unique characteristic that both scans occurred within the same week in 89 % of the patients and in the other 11 % only minor time differences were noticed; therefore the results will not be influenced by time effects. The protocol is also prospective for both scans. Finally and probably most importantly, during the comparison, ^{111}In-pentetreotide was systematically favoured over ^{68}Ga-DOTATOC (a) using SPECT-images for PET-comparison leading to a pure tomographic comparison, (b) using non-attenuation-corrected (NAC) images on PET as ^{111}In-pentetreotide SPECT-images are intrinsically not corrected for attenuation and (c) because we did not perform a blind scoring of the ^{111}In-pentetreotide scans, but we retrospectively re-evaluated the scans in case discordant lesions were found on ^{68}Ga-DOTATOC PET; if those lesions could not be identified on the other modality, only then were they categorized as incremental lesions.

In Figs. 3 and 4, the attenuation corrected images are also shown; we observed no difference in lesion detection compared to the non-attenuation-corrected images. A limitation of our study was the absence of verification by histopathology; however, histopathological confirmation of the NET was already performed at initial staging in all patients.

Finally, the clinical impact in this study population is difficult to analyse as all study patients were documented with overt metastatic disease and were already planned for PRRT. Possible treatment changes from the use of ^{68}Ga-DOTATOC PET compared to ^{111}In-pentreotide SPECT could be assumed in seven of the 53 patients (13 %). This is probably even an underestimation of the impact of PET as this study population had a high tumour burden with limited impact of additional lesions and only a limited part of the body was compared.

Conclusion

^{68}Ga-DOTATOC-PET is superior to ^{111}In-pentetreotide-scintigraphy SPECT for the detection of NET metastases, detecting a significantly higher number of tumoral lesions, especially in the skeleton and the liver. ^{68}Ga-DOTA-peptide PET is the nuclear medicine imaging method of choice for accurate depiction of NET tumour burden.

Acknowledgments The scientific guarantor of this publication is Christophe M. Deroose. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. This study has received funding from the Instituut voor de Aanmoediging van Innovatie door Wetenschap en Technologie in Vlaanderen (IWT) http://www.iwt.be ; PROTOCOL: IWT-TBM Project: 0707181. Dr. K. Bogaerts, an profession expert on biostatistics from the Division of Public Health and primary Care (I-biostat), KU Leuven, Belgium is co-author of the article and provided statistical advice for this manuscript. Institutional Review Board approval was obtained from the ethics committee of the university hospitals and university of Leuven. Written informed consent was obtained from all subjects (patients) in this study.

Some results from this cohort have already been published. No data regarding the topic of this article, the comparison of diagnostic accuracy between ^{68}Ga-DOTATOC and ^{111}In-pentreotide, has been previously published. These findings are the integral and definitive results of this section of our prospective study, no other publications regarding this topic will follow. We published two case reports about two patients in this cohort. The first case report discusses the aberrant distribution of ^{68}Ga-DOTATOC 7 weeks after one cycle of PRRT [1]. The second case report discusses the impact of renal insufficiency on kidney dose after PRRT [2]. Both these topics are unrelated to the diagnostic accuracy of the imaging methods. We also published results of the limited nephrotoxicity after PRRT using kidney dosimetry to modulate the administered activity to the patients [3]. This topic as well is fully unrelated to the diagnostic accuracy of the imaging methods discussed in the current manuscript.

Methodology: prospective, experimental, performed at one institution.

References

1. Modlin IM, Oberg K, Chung DC et al (2008) Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 9:61–72
2. Reubi JC, Schar JC, Waser B et al (2000) Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 27:273–282
3. Reubi JC, Waser B (2003) Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. Eur J Nucl Med Mol Imaging 30:781–793
4. Kwekkeboom DJ, Kooij PP, Bakker WH et al (1999) Comparison of 111In-DOTA-Tyr3-octreotide and 111In-DTPA-octreotide in the same patients: biodistribution, kinetics, organ and tumor uptake. J Nucl Med 40:762–767
5. Imhof A, Brunner P, Marincek N et al (2011) Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 29:2416–2423
6. Kwekkeboom DJ, de Herder WW, Kam BL et al (2008) Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 26: 2124–2130
7. Hofmann M, Maecke H, Borner R et al (2001) Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med 28:1751–1757
8. Kwekkeboom DJ, Krenning EP, Scheidhauer K et al (2009) ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: somatostatin receptor imaging with (111)In-pentetreotide. Neuroendocrinology 90:184–189
9. Haug AR, Cindea-Drimus R, Auernhammer CJ et al (2012) The Role of 68Ga-DOTATATE PET/CT in Suspected Neuroendocrine Tumors. J Nucl Med 53:1686–1692
10. Koukouraki S, Strauss LG, Georgoulias V et al (2006) Evaluation of the pharmacokinetics of 68Ga-DOTATOC in patients with metastatic neuroendocrine tumours scheduled for 90Y-DOTATOC therapy. Eur J Nucl Med Mol Imaging 33:460–466
11. Teunissen JJ, Krenning EP, de Jong FH et al (2009) Effects of therapy with [177Lu-DOTA 0, Tyr 3]octreotate on endocrine function. Eur J Nucl Med Mol Imaging 36:1758–1766
12. Gabriel M, Decristoforo C, Kendler D et al (2007) 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 48:508–518
13. Buchmann I, Henze M, Engelbrecht S et al (2007) Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 34:1617–1626
14. Srirajaskanthan R, Kayani I, Quigley AM et al (2010) The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. J Nucl Med 51:875–882
15. van Essen M, Krenning EP, Kam BL et al (2009) Peptide-receptor radionuclide therapy for endocrine tumors. Nat Rev Endocrinol 5: 382–393
16. Meyer GJ, Macke H, Schuhmacher J et al (2004) 68Ga-labelled DOTA-derivatised peptide ligands. Eur J Nucl Med Mol Imaging 31:1097–1104
17. Van Binnebeek S, Deroose CM, Baete K et al (2011) Altered biodistribution of somatostatin analogues after first cycle of Peptide receptor radionuclide therapy. J Clin Oncol 29:e579–e581
18. Van Binnebeek S, Baete K, Terwinghe C et al (2013) Significant impact of transient deterioration of renal function on dosimetry in PRRT. Ann Nucl Med 27:74–77
19. Van Binnebeek S, Baete K, Vanbilloen B et al (2014) Individualized dosimetry-based activity reduction of (9)(0)Y-DOTATOC prevents severe and rapid kidney function deterioration from peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging 41:1141–1157
20. Kowalski J, Henze M, Schuhmacher J et al (2003) Evaluation of positron emission tomography imaging using [68Ga]-DOTA-D Phe(1)-Tyr(3)-Octreotide in comparison to [111In]-DTPAOC SPECT. First results in patients with neuroendocrine tumors. Mol Imaging Biol 5:42–48
21. Geijer H, Breimer LH (2013) Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 40:1770–1780
22. Treglia G, Castaldi P, Rindi G et al (2012) Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. Endocrine 42:80–87
23. Schreiter NF, Brenner W, Nogami M et al (2012) Cost comparison of 111In-DTPA-octreotide scintigraphy and 68Ga-DOTATOC PET/CT for staging enteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 39:72–82