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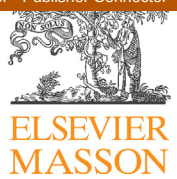

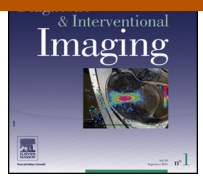

ORIGINAL ARTICLE / *Oncology*

Peptide receptor radionuclide therapy of neuroendocrine tumors with ^{90}Y-DOTATOC: Is treatment response predictable by pre-therapeutic uptake of ^{68}Ga-DOTATOC?

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KEYWORDS
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Abstract
Purpose: PET with ^{68}Ga-DOTATOC allows for imaging and quantitative assessment of somatostatin receptor expression in neuroendocrine tumors (NET). The aim of this retrospective study was to analyze whether pre-therapeutic ^{68}Ga-DOTATOC PET/CT is able to predict response to Peptide Receptor Radionuclide Therapy (PRRT).
Patients and methods: Forty patients with advanced stage NET were treated with a fixed dose of ^{90}Y-DOTATOC (5550 or 3700 MBq). Prior to PRRT, each patient received ^{68}Ga-DOTATOC PET/CT. Treatment results were evaluated after 3 months by CT, tumor marker levels and clinical course and correlated with ^{68}Ga-DOTATOC uptake (SUVmax) and the assumed uptake of ^{90}Y-DOTATOC in tumor manifestations (MBq/g). ROC analysis and pairwise comparison of area under the curve (AUC) were performed with pre-treatment uptake of ^{68}Ga-DOTATOC, assumed uptake of ^{90}Y-DOTATOC and treatment activity alone and in relation to body weight as continuous variables, and response/no response as classification variable.

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Results: According to conventional criteria (tumor shrinkage, decrease of tumor markers, improved or stable clinical condition), 20 patients were classified as responders, 16 as non-responders and in four patients findings were equivocal. Using a SUV more than 17.9 as cut-off for favorable outcome, PET was able to predict treatment response of all responders and 15 out of 16 non-responders. All four patients with equivocal findings showed SUV less than or equal to 17.9 and soon experienced tumor progression. The assumed uptake of ^{90}Y-DOTATOC in tumor manifestations using a cut-off more than 1.26 MBq/g as predictor of response was able to correctly classify 19 out of 20 responders, and 14 out of 16 non-responders. In all patients with equivocal findings, the assumed uptake of ^{90}Y-DOTATOC was below 1.26 MBq/g.
Conclusion: Pre-therapeutic ^{68}Ga-DOTATOC tumor uptake as well as assumed uptake of ^{90}Y-DOTATOC are strongly associated with the results of subsequent PRRT. The defined cut-off values should be confirmed by prospective studies and may then provide the rationale for individual dosing and selecting patients with high likelihood of favorable treatment outcome.

Neuroendocrine tumors (NET) are relatively rare neoplasms, mainly originating from the digestive system. Usually they tend to be well differentiated and consecutively slow progressing. At the time of diagnosis, they are often in an inoperable or advanced stage with multiple lymph node and/or distant metastases [1—7].

Since therapeutic options are limited and cure rates are low, localization and assessment of disease extent are crucial for the clinical management of NET. Commonly used diagnostic modalities include morphological imaging procedures like ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), and functional imaging techniques, including the use of somatostatin receptor scintigraphy with e.g. ^{111}Indium DTPA octreotide or ^{99}mTc-EDDA/HYNIC-octreotate, and positron emission tomography with ^{68}Ga-somatostatin analogues.

Treatment is multidisciplinary and should be individualized according to the tumor type, burden, and symptoms. Therapeutic tools include surgery, interventional radiology (e.g. chemoembolisation and radiofrequency ablation), medical treatment such as somatostatin analogues (e.g. octreotide or lanreotide), interferon α, chemotherapy, radiotherapy (e.g. of symptomatic spine lesions) as well as targeted treatments with multi-tyrosine kinase inhibitors (e.g. sunitinib) or mTOR (mammalian target of rapamycin) inhibitors like everolimus, and peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogues [8—11].

NET are characterized by the over-expression of somatostatin receptors (SSTR) on the cell membrane, thus enabling the therapeutic use of somatostatin analogues, which have been shown to be able to reduce signs and symptoms of hormone hypersecretion, improve quality of life, and slow tumor growth. Although the subtypes and number of SSTR expressed in neoplastic cells can be variable, subtype 2 is clearly predominant [12]. Expression of these specific receptors forms the molecular basis for the successful use of radiolabeled somatostatin analogues, both for imaging and therapy [13,14].

PRRT with radiolabelled somatostatin analogues such as ^{90}Yttrium-DOTA^{0}-*D*-Phe^{1}-Tyr^{3}-octreotide (^{90}Y-DOTATOC) has been explored in NET for more than a decade and is a promising treatment modality in the management of patients with inoperable or metastasized NET [15—17]. Present knowledge and clinical studies indicate that these radiopharmaceuticals are able to irradiate tumors and their metastases via internalization through SSTR (mainly subtype 2). PRRT can deliver radiation doses to tumors, which are adequate to achieve significant volume reduction with partial and complete objective responses in up to 30% of patients [18,19]. Side effects, involving kidneys and bone marrow, are mild, if adequate renal protection is used [20]. A consistent survival benefit is reported with morphologic and biochemical response to PRRT as well as significant improvement of quality of normal daily life [21—24].

In clinical routine, morphological imaging procedures, particularly CT and MRI, are well established for the evaluation of therapy response. The assessment of treatment outcome for solid tumors is based on the Response Evaluation Criteria in Solid Tumors (RECIST), defining response as a 30% decrease in the largest diameter of the tumor [25,26].

NET are generally rather heterogeneous in terms of pathomorphology, biologic behavior, and peptide receptor expression, i.e. in some tumor areas a high receptor density may be found whereas other areas lack receptors. Internal radiation therapy with high-energy β-emitters (e.g. ^{90}Y) induces damage to tumor cells during a relatively long period of time. Thus, tumor shrinkage may be small or even not detectable although tumor cells are replaced by necrotic and fibrotic tissue. The distribution of radiation dose throughout a tumor depends on tumor size, the radionuclide used and its intratumoral distribution. Factors such as biologic properties of the tumor, affinity of targeting molecules to tumor cells, and extent and permeability of the tumor vasculature determine the distribution of targeting molecules within the tumor. Furthermore, the physical characteristics of the radionuclides delivered by the targeting molecules have a significant influence, particularly the energy spectrum of the ionizing particles, which determines the range of the energy emission. Radiosensitivity, repair capacity, proliferation rate and induction of apoptosis after low-dose radiation are additional factors that impose a further level of variability to the response of tumor cells to radiation [27—30].

SSTR-based functional imaging, such as ^{68}Ga-DOTATOC PET, allows for imaging and quantitative assessment of

radioactivity distribution, in particular binding to somatostatin receptors in tumor manifestations as well as in normal tissue [31—33].

The aim of this retrospective study was to analyze whether response to PRRT is correlated to pre-therapeutic tumor uptake of ^{68}Ga-DOTATOC and to the assumed uptake of ^{90}Y-DOTATOC within the tumor and if so, whether cut-off values for ^{68}Ga-DOTATOC uptake and assumed ^{90}Y-DOTATOC uptake can be defined to predict favorable outcome of PRRT.

Materials and methods

Patients

A total of 40 consecutive patients (23 men, 17 women; age 30—79 years, mean ± SD: 61.3 ± 11.6) with advanced stage NET, treated between November 2004 and November 2008, were included in this retrospective study: 12 patients with NET of pancreatic origin, 14 patients with NET of the intestine (small or large bowel), one of bronchial origin, nine patients with NET of unknown primary, one patient with glucagonoma, one patient with medullary thyroid cancer, one patient with medullary thymoma and one patient with phaeochromocytoma.

In all patients, a NET was histologically confirmed as well as progressive disease on the basis of previous morphological imaging. SSTR-expression was documented by ^{68}Ga-DOTATOC PET in all patients. In this group of advanced tumors, various therapeutic procedures had been performed prior to PRRT. Seventeen patients were treated with surgery alone, three patients had received additional chemotherapy and one patient radiofrequency ablation of liver metastases after surgery, five patients were so far treated by chemotherapy alone, one patient had surgery, radiotherapy of spine lesions and radiofrequency ablation of liver metastases, one patient was treated with chemoembolisation of liver metastases, and 19 patients received long-acting somatostatin analogues alone or in combination with interferon-α. Patient characteristics, localization of primary tumors and pre-treatment are listed in Table 1.

This retrospective study was approved by the local ethical committee and written informed consent was obtained from all patients before they were enrolled in the study.

PRRT

The patients were hospitalized for 48 h in accordance with the legal requirements for radiation protection. A uniform application protocol with fixed radioactivity doses was used. In 19 patients, 5550 MBq (5300—6350 MBq, mean ± SD, 5759.4 ± 242.5) and in 21 patients, 3700 MBq (3350—3910 MBq, mean ± SD, 3712 ± 131.3) were injected. Intravenous infusion of 2000 mL of amino acid solution (Ringer's lactated Hartmann solution, Proteinsteril [B. Braun Medical AG, Sempach, Switzerland] HEPA 8%, Mg 5-Sulfat [B. Braun Medical AG, Sempach, Switzerland]) to inhibit tubular reabsorption of the radiopeptide was started 30 min before and continued until 3 h after treatment [34,35].

During the evaluation period, the radioactivity dose was reduced from 5550 MBq (n = 19) to 3700 MBq (n = 21) according to consensus of a joint workshop of the German Society of Nuclear Medicine and the German Society of Endocrinology in 2006 in order to standardize therapy protocols.

^{68}Ga-DOTATOC PET/CT

DOTA^0-D-Phe^1-Tyr^3-octreotide (DOTATOC) was provided by JPT (Berlin, Germany). ^{68}Ga-Generators (TiO_2 phase based) from Cyclotron Co. Ltd., Russia, were used (1110 or 1850 MBq). HCl (37%), water for trace analysis and acetone were purchased from Fluka (Germany) and of highest purity available (minimum traces of metals). ^{68}Ga-DOTATOC was synthesized as described previously in a home-made manually operable synthesizing device [36].

Each patient received a ^{68}Ga-DOTATOC PET/CT scan before (i.e. 1 to a maximum of 3 days) and 3 months after PRRT. Long-acting somatostatin analogues were discontinued for at least 6 weeks before initial and follow-up PET/CT scans.

PET/CT imaging started 20 min after administration of 150—170 MBq of ^{68}Ga-DOTATOC. The examinations were performed using the Hi-Rez Biograph 16 PET/CT device (Siemens Medical Solutions, Knoxville, USA), consisting of a high-resolution 3D LSO PET and a state-of-the-art 16-row multi-detector CT (MDCT). The non-enhanced CT data were used for attenuation correction of PET emission images. PET images were reconstructed using an iterative algorithm (ordered-subset expectation maximization: 2 iterations, 8 subsets). To obtain diagnostic CT data, in all patients a multi-phase CT protocol with intravenous administration of 120 mL iodinated contrast agent (Ultravist 370, Schering, Berlin, Germany) at a flow of 2—3 mL/s was performed.

Assessment of laboratory parameters

Chromogranin A, neuron-specific enolase (NSE) and serotonin were measured in all patients. Calcitonin was assessed only in one patient (patient No. 28, medullary thyroid cancer). NSE was measured by a non-competitive immunoassay based on time-resolved amplified cryptate emission (TRACE) technology (Brahms, Henningsdorf, Germany). Chromogranin A and calcitonin were determined using an enzyme-linked immuno sorbent assay (ELISA; Dako, Glostrup, Denmark). Serotonin was measured by high-pressure liquid chromatography (HPLC; Chromsystems, Munich, Germany).

Follow-up

PET/CT images were interpreted by two experienced nuclear medicine physicians and two experienced radiologists in consensus, each having more than 10 years experience in oncological imaging. The interpreters had access to all clinical information.

Distribution of ^{68}Ga-DOTATOC was evaluated visually and semi-quantitatively using standard uptake values (SUVmax) normalized for body weight. The criterion for malignancy was focally increased uptake higher than that of the liver. Number, uptake (PET) and size (CT) of lesions were determined. For each patient, a reference lesion, which was best visible, easy to define and more than or equal to 1.5 cm in diameter was assigned for follow-up (PET: comparison of pre- and post-therapeutic SUVmax). The assumed uptake of

Table 1 Patient characteristics.

No	Location of primary NET	PRRT [MBq]	Response				^{68}Ga	^{90}Y	Activity/body weight	Pre-treatment
			PET	CT	Tumor marker	Clinical course				
1	Pancreas	5661	(−)	(−)	(−)	(−)	36.6	3.6999	101.09	CTx, SA
2	Pancreas	5875	(−)	(−)	(−)	(−)	23.8	2.8363	119.17	CTx, SA
3	Ileocecal valve	6100	(−)	(−)	(−)	(−)	31.3	2.3284	74.39	OP, SA
4	Pancreas	3730	(−)	(−)	(−)	(−)	53.3	2.2338	41.91	SA
5	Pancreas	3794	(−)	(−)	(−)	(−)	52.1	2.4711	47.43	CTx
6	Pancreas	3760	(−)	(−)	(−)	(−)	39.6	2.0394	51.5	CE, SA
7	Pancreas	3730	(−)	(−)	(−)	(−)	29.8	2.0973	45.48	CTx
8	Jejunum	3750	(−)	(−)	(−)	(−)	34.5	2.3522	68.18	OP
9	Pancreas	3760	(−)	(−)	(−)	(−)	36.4	1.9834	54.49	None
10	Ileum	3700	(−)	(−)	(−)	(−)	30.4	0.9098	30.33	None
11	Coecum	5800	(−)	SD	(−)	(−)	25.7	2.4436	95.08	OP
12	Bronchus	5650	(−)	SD	(−)	(−)	33.6	2.8765	85.61	OP, SA
13	Pancreas	5940	(−)	SD	(−)	(−)	20.3	2.3877	117.62	SA and IF
14	Unknown primary	5300	(−)	SD	(−)	(−)	21.7	1.9168	88.33	None
15	Pancreas	3730	(−)	SD	(−)	(−)	28.7	2.0199	70.38	SA
16	Ileum	3714	(−)	SD	(−)	(−)	31.3	1.6607	53.10	OP, SA
17	Jejunum	3910	(−)	SD	(−)	(−)	22.5	1.2938	57.50	None
18	Pancreas	3340	(−)	SD	(−)	(−)	35.6	1.303	36.3	None
19	Pancreas	3773	(−)	SD	(−)	(−)	34.9	1.2886	37.36	OP
20	Glucagonoma	6350	(−)	SD	(−)	(−)	20.4	1.9627	96.21	OP
21	Ileum	5481	(+)	SD	(−)	(−)	11.4	1.0414	91.35	OP, SA
22	Unknown primary	3670	(+)	SD	(−)	(−)	16	0.9626	60.16	SA
23	Ileocecal valve	3350	(+)	SD	(−)	SD	3.5	0.1379	39.41	OP, SA
24	Ileum	3815	(+)	SD	(−)	SD	17.9	0.9618	53.73	OP, SA
25	Thymus	5683	SD	(+)	(+)	(+)	3.7	0.3286	88.8	OP, SA
26	Coecum	5855	(+)	(+)	(+)	(+)	15.4	1.4088	91.48	OP
27	Unknown primary	5416	(+)	(+)	(+)	(+)	26.7	2.2954	85.97	SA
28	Thyroid (medullary)	5650	(+)	(+)	(+)	(+)	6.7	0.6106	91.13	OP, CTx
29	Rectum	5900	(+)	(+)	(+)	(+)	13.2	0.9055	68.6	OP
30	Pancreas	5621	(+)	(+)	(+)	(+)	13.4	0.8463	63.16	OP, RFA, SA
31	Unknown primary	3729	(+)	(+)	(+)	(+)	7.1	0.3894	54.84	OP, CTx
32	Unknown primary	3757	(+)	(+)	(+)	(+)	5.8	0.3352	57.8	OP, RFA, RT (spine)
33	Unknown primary	5910	(+)	(+)	(+)	(+)	13.6	1.0438	76.75	OP, CTx, SA

Table 1 (*Continued*)

No	Location of primary NET	PRRT [MBq]	Response				^{68}Ga	^{90}Y	Activity/body weight	Pre-treatment
			PET	CT	Tumor marker	Clinical course				
34	Unknown primary	5630	(+)	(+)	(+)	(+)	16.2	1.1123	68.66	None
35	Pheochromocytoma	5870	(+)	(+)	(+)	(+)	9.4	0.726	77.23	OP
36	Ileum	5736	(+)	(+)	(+)	(+)	16.5	1.2619	76.48	OP, SA
37	Unknown primary	3755	(+)	(+)	(+)	(+)	11.6	0.6406	55.22	SA
38	Ileocecal valve	3711	(+)	(+)	(+)	(+)	9.1	0.4966	54.57	OP, SA
39	Ileum	3726	(+)	(+)	(+)	(+)	7	0.3952	56.46	OP
40	Unknown primary	3756	(+)	(+)	(+)	(+)	5.7	0.2933	51.45	CTx

PRRT: peptide receptor radionuclide therapy; ^{68}Ga: pre-therapeutic ^{68}Ga-DOTATOC uptake [SUVmax]; ^{90}Y: pre-therapeutic assumed ^{90}Y-DOTATOC uptake [MBq/lesion (g) $\times$ SUVmax]; CTx: chemotherapy; SA: somatostatin analogues; OP: operation; CE: chemoembolization; IF: interferon-α; RFA: radiofrequency ablation; RT: radiotherapy; SD: stable disease.
($-$): regression: PET (SUVmax decrease of more than 15%); CT (decrease of tumor size or stable disease according to RECIST criteria), tumor marker (decrease of more than 15%); clinical course (weight gain, improvement of clinical symptoms).
(+): progression: PET (SUVmax increase of more than 15% and/or new lesion(s)); CT (increase of tumor size according to RECIST), tumor marker (increase of more than 15%); clinical course (weight loss, deterioration of clinical symptoms).

^{90}Y-DOTATOC within the reference lesion was assessed by the administered treatment radioactivity [MBq] divided by the body weight [g] and multiplied by the SUVmax of ^{68}Ga-DOTATOC uptake. Response Criteria In Solid Tumors (RECIST) was used for CT to evaluate tumor response to treatment.

In all patients, plasma levels of chromogranin A, neuron-specific enolase, and serotonine were measured pre-therapeutically. For follow-up, only those tumor markers with increased pre-therapeutic plasma levels were used. In only one patient calcitonin was assessed pre- and post-therapeutically (patient No. 28, medullary thyroid cancer). For the evaluation of clinical course, we assessed the general condition, weight gain or loss, and symptoms (e.g. flush, diarrhea, abdominal discomfort) pre- and post-treatment.

Treatment results were evaluated after 3 months by CT, tumor markers (chromogranin A, serotonin, neuron-specific enolase [NSE], calcitonin), and clinical course and correlated with pre-therapeutic ^{68}Ga-DOTATOC uptake (SUVmax) and the assumed uptake of ^{90}Y-DOTATOC (MBq/g) in tumor manifestations. Tumor regression was defined as decrease of SUVmax of more than 15% (PET), decrease of tumor size or stable disease (CT) according to RECIST criteria, descent of tumor marker of more than 15% and improvement of clinical symptoms or weight gain. Progression of disease was defined as increase of SUVmax of more than 15% and/or new lesion(s) (PET); increase of tumor size (CT) according to RECIST criteria, rising tumor marker of more than 15%, and deterioration of clinical state (weight loss, and/or worsening of clinical symptoms).

Statistical analysis

Albeit a limited number of cases per group, a ROC analysis was performed with pre-treatment uptake of ^{68}Ga-DOTATOC, estimated ^{90}Y-DOTATOC uptake, treatment radioactivity and treatment radioactivity to body weight ratio as continuous variables, and response/no response as classification variable. To find diagnostic cut-off values treatment response beyond doubt, four patients with equivocal clinical, CT and laboratory findings, but increasing ^{68}Ga-DOTATOC uptake during follow-up were included in the non-responder group.

ROC analysis was done according to the method proposed by Hanley and McNeil, with calculation of Youden-index and area under the curve (AUC), including standard error and significance level, i.e. maximum attainable discrimination and the utilization of radiological examinations [37]. AUC for pre-treatment uptake of ^{68}Ga-DOTATOC, estimated ^{90}Y-DOTATOC uptake, treatment radioactivity and treatment to body weight ratio was compared pairwise. All calculations were executed with MedCalc®, Version 11.0.

Results

Response assessment 3 months after PRRT

According to conventional criteria (tumor shrinkage, decrease of tumor markers, improving or stable clinical condition), 20 patients were classified as responders, 16 as non-responders. In four patients, follow-up findings were equivocal, i.e. PET demonstrated increase of ^{68}Ga-DOTATOC uptake, whereas CT and the clinical condition were stable, and tumor markers were falling. There was no relevant difference with regard to pre-treatment and/or tumor burden in responders or non-responders (Table 1).

Responders (example shown in Fig. 1, patient No. 4) included 11 patients with NET originating from the pancreas, six from the intestine (two jejunum, two ileum, one ileocecal valve, one coecum), one from the bronchus, one from unknown site, and one glucagonoma.

The group of non-responders (example shown in Fig. 2, patient No. 37) comprised seven patients with NET of

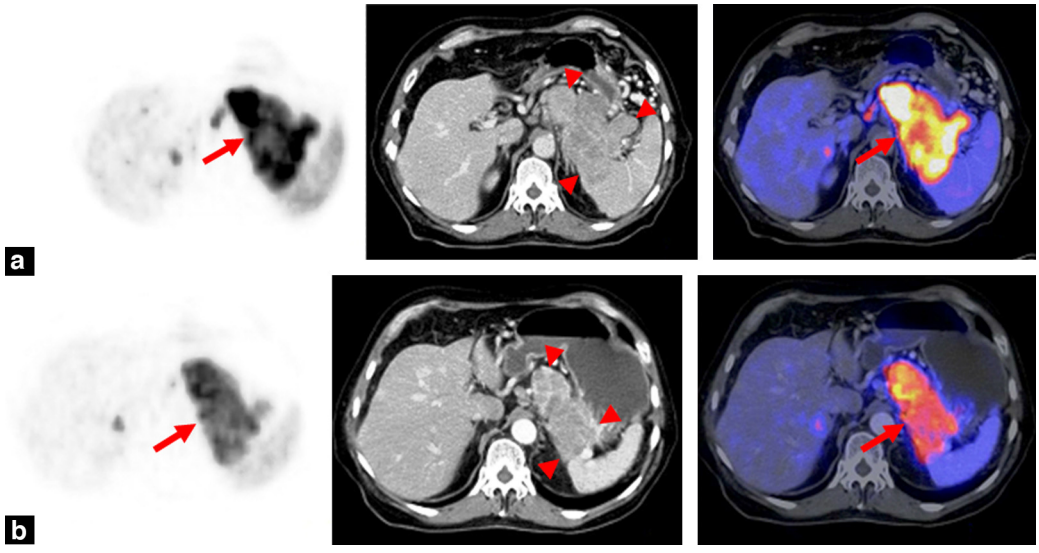

Figure 1. Responder to peptide receptor radionuclide therapy (PRRT). A 63-year-old man with metastasized neuroendocrine tumor of the pancreas (PET, CT, and Fusion). Before (a) and after (b) PRRT with 3730 MBq ^{90}Y-DOTATOC. Post-therapeutic decrease of ^{68}Ga-DOTATOC uptake (arrows), reduction of tumor size (arrowheads), falling tumor markers and improving general condition with weight gain reflecting good treatment response. Pre-therapeutic ^{68}Ga-DOTATOC uptake was 53.3; pre-therapeutic assumed ^{90}Y-DOTATOC uptake was 2.2 MBq/g.

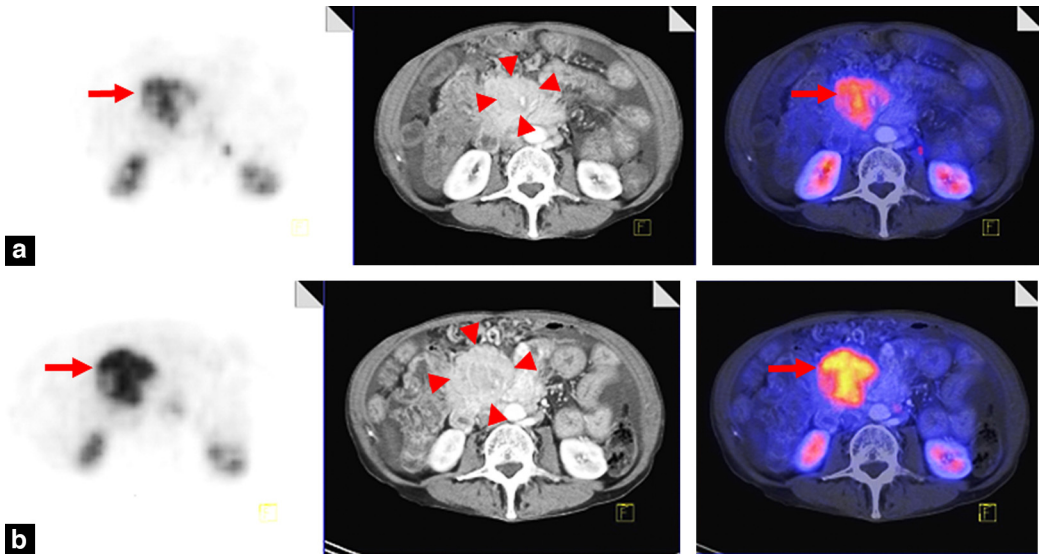

Figure 2. Non-responder to PRRT. A 62-year-old woman with metastasized neuroendocrine tumor of unknown origin (PET, CT, and Fusion). Before (a) and after (b) PRRT with 3755 MBq ^{90}Y-DOTATOC. Post-therapeutic increase of ^{68}Ga-DOTATOC uptake (arrows) and of tumor size (arrowheads), rising tumor markers and deterioration of clinical condition with weight loss. Pre-therapeutic ^{68}Ga-DOTATOC uptake was 11.6; pre-therapeutic assumed ^{90}Y-DOTATOC uptake was 0.6 MBq/g.

unknown origin, five of the intestine (two ileum, one ileocoecal valve, one coecum, and one rectum), one of the pancreas, one phaeochromocytoma, one medullary thymoma, and one medullary thyroid cancer.

One patient with NET of unknown primary and three patients with intestinal NET (two ileum, one ileocoecal valve) revealed equivocal findings. However, further follow-up of these patients confirmed tumor progression (CT, tumor markers) with clinical deterioration after 9 months (patient No. 24; Fig. 3), 10 months (patient No. 22), 12 months (patient No. 21), and 16 months (patient No. 23). Of the responders, only one patient had a recurrence after 24 months (patient No. 1).

Of 19 patients who were treated with 5550 MBq (5300—6350 MBq, mean ± SD, 5759.4 ± 242.5), eight were classified as responder, 10 as non-responder, and one patient revealed equivocal findings. The NET of this group were of pancreatic and unknown origin, both in four patients, of intestinal origin in six patients (two ileum, one ileocoecal valve, two coecum, one rectum), and five other NET (bronchus, glucagonoma, thymus, thyroid, phaeochromocytoma).

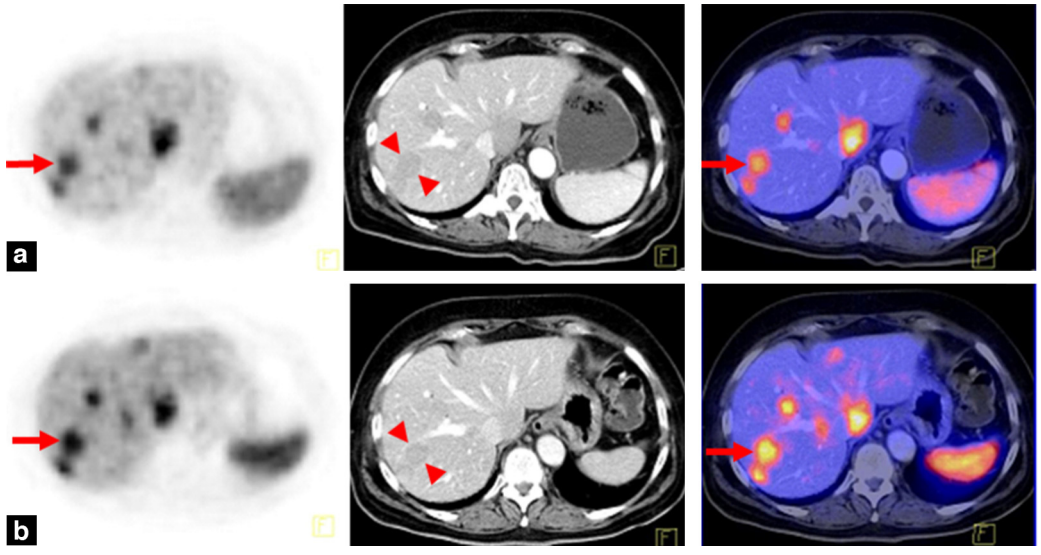

Figure 3. Equivocal findings after PRRT. A 60-year-old woman with metastasized neuroendocrine tumor of the ileum (PET, CT, and Fusion). Before (a) and after (b) PRRT with 3815 MBq ^{90}Y-DOTATOC. Post-therapeutic equivocal findings with increase of ^{68}Ga-DOTATOC uptake (arrows), but morphologically stable disease (arrowheads), falling tumor markers and good general condition. Follow-up showed tumor progression (CT, tumor markers, clinical condition) after 9 months. Pre-therapeutic ^{68}Ga-DOTATOC uptake was 17.9; pre-therapeutic assumed ^{90}Y-DOTATOC uptake was 1.0 MBq/g.

PRRT with 3700 MBq (3350—3910 MBq, mean ± SD, 3712 ± 131.3) was performed in 21 patients. In this group, we found 12 responders, six non-responders, and three patients with equivocal findings. The tumors comprised pancreatic NET ($n = 8$), intestinal NET ($n = 8$; two jejunum, four ileum, two ileocecal valve), and five patients with NET of unknown origin.

Statistical results

^{68}Ga-DOTATOC uptake

As illustrated in Fig. 4a and b, ^{68}Ga-DOTATOC PET with use of an SUVmax more than 17.9 (calculated Youden-index) as cut-off facilitates separation of treatment responders (SUVmax ranging from 20.3 to 53.3, mean ± SD, 32.13 ± 9.12) from non-responders (in 15/16: SUVmax 3.7 to 16.5, mean ± SD, 11.32 ± 5.59) with a sensitivity of 100% and specificity of 95% (95% CI 83.2—100 and 75.1—99.9, respectively). Only one non-responder presented with SUVmax more than 17.9 (patient No. 27, SUVmax 26.7). All patients with equivocal findings had SUVmax less or equal to 17.9 (SUVmax 3.5, 11.4, 16.0, 17.9; mean ± SD, 12.2 ± 6.41).

Assumed tumor uptake of ^{90}Y-DOTATOC

As surrogate of the achieved target dose, the assumed tumor uptake of ^{90}Y-DOTATOC (Fig. 5a and b) was calculated as treatment radioactivity [MBq]/body weight [g] × SUVmax. By calculating a threshold of more than 1.26 MBq/g (Youden-index) for positive therapy response, 19 out of 20 responders could be correctly identified (1.28 to 3.69 MBq/g, mean ± SD, 2.17 ± 0.59). Only one patient revealed a lower tumor uptake with 0.91 MBq/g (patient 10). Of the non-responders, 14 out of 16 were correctly classified (0.29 to 1.26 MBq/g, mean ± SD, 0.67 ± 0.32), only two patients showed higher tumor uptake with 2.29 MBq/g (patient 27) and 1.41 MBq/g (patient 26). All patients with equivocal findings were below 1.26 MBq/g (0.13 to 1.04 MBq/g, mean ± SD, 0.78 ± 0.43).

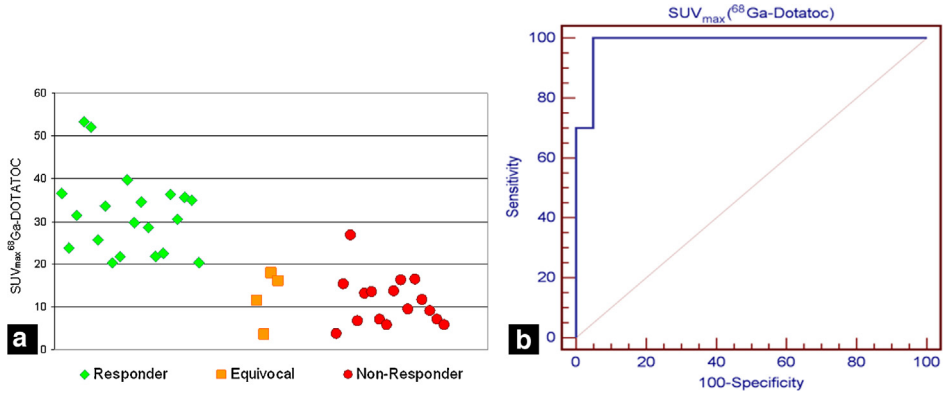

Figure 4. Pre-therapeutic uptake of ^{68}Ga-DOTATOC with SUVmax more than 17.9 as cut-off value (calculated Youden-index) for therapy response. All responders were above this threshold. Fifteen out of 16 non-responders showed an SUV less than 17.9, only one non-responder revealed higher ^{68}Ga-DOTATOC uptake (SUVmax 26.7), sensitivity 100% and specificity 95%. Patients with equivocal findings revealed an SUVmax less or equal to 17.9, and follow-up of these patients confirmed significant tumor progression (CT, tumor markers) and clinical deterioration.

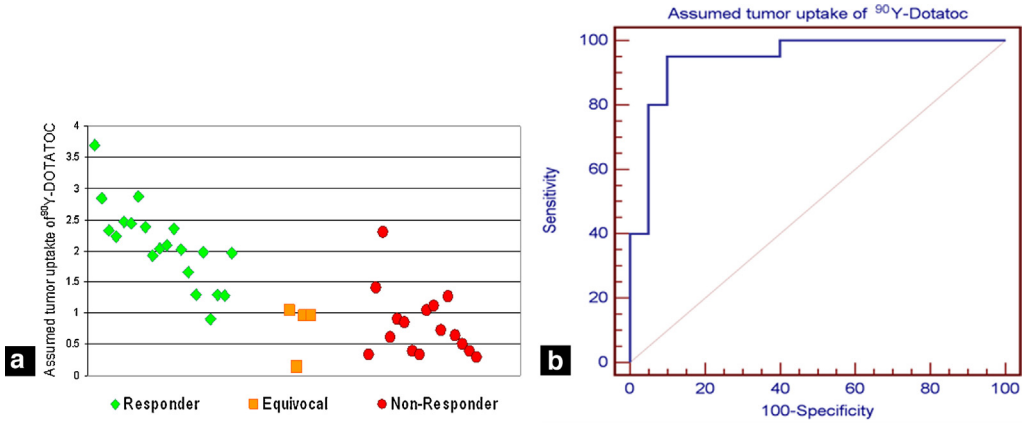

Figure 5. Assumed tumor uptake of ^{90}Y-DOTATOC (treatment activity [MBq]/body weight [g] × SUVmax). Nineteen out of 20 responders were correctly predicted using more than 1.26 MBq/g as cut-off value, only one patient revealed lower tumor uptake (0.9 MBq/g). Fourteen out of 16 non-responders were correctly identified, only two patients presented with higher assumed tumor uptake of ^{90}Y-DOTATOC (patient 27 with 2.29 MBq/g, and patient 26 with 1.41 MBq/g). All patients with equivocal findings were below the limit of 1.5 MBq/g, and follow-up of these patients confirmed significant tumor progression (CT, tumor markers) and clinical deterioration.

Treatment radioactivity

The applied treatment radioactivity [MBq] alone (Fig. 6a and b) or in relation to body weight [MBq]/[kg] (Fig. 7a and b) without considering specific tumor uptake measured by ^{68}Ga-DOTATOC PET/CT did not reveal any correlation to therapy response. Consequently, pairwise comparison of AUC revealed significant differences ($P < 0.001$) between applied treatment radioactivity and ^{68}Ga-DOTATOC uptake as well as assumed tumor uptake of ^{90}Y-DOTATOC. No significant difference was found between AUC of ^{68}Ga-DOTATOC uptake and assumed tumor uptake of ^{90}Y-DOTATOC.

Discussion

For clinical management, somatostatin receptor based functional imaging has become standard for staging and restaging. It allows sensitive localization of tumor manifestations and selection of patients eligible for peptide receptor radionuclide therapy [38,39].

Because NET are generally slow progressing, they are often diagnosed in highly advanced or even inoperable stage. In this situation, treatment options are limited. Trials with long-acting somatostatin analogues, interferon-α, or chemotherapy have shown low response rates with regard to cytoreduction [23,40].

In the past few years, treatment studies with somatostatin-based radioligands like ^{90}Y-DOTATOC have been conducted with encouraging overall results, although reported percentages of tumor remission after PRRT vary considerably [13,41,42]. The overall response rates of our study are comparable to those reported in the literature. Possible reasons for this variation of therapy outcome include different administered doses and dosage schemes, e.g. some studies use dose-escalating schemes, whereas others use fixed doses. On the other hand, tumor characteristics (e.g. the uptake on pre-therapeutic functional imaging with somatostatin analogues, the estimated total tumor burden, or extent of liver involvement) may strongly influence treatment outcome. Besides, differences in patient selection may also play an important role. Therefore, standardization of patient selection, therapy protocols and adequate methods for assessing therapy response are required [43].

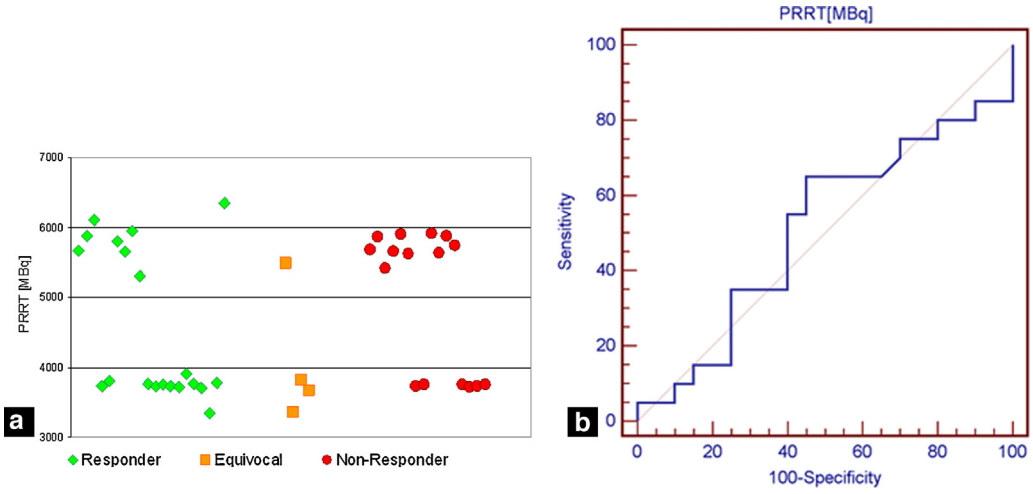

Figure 6. The applied treatment radioactivity alone without considering specific tumor uptake measured by ^{68}Ga-DOTATOC PET/CT did not reveal any correlation with therapy response.

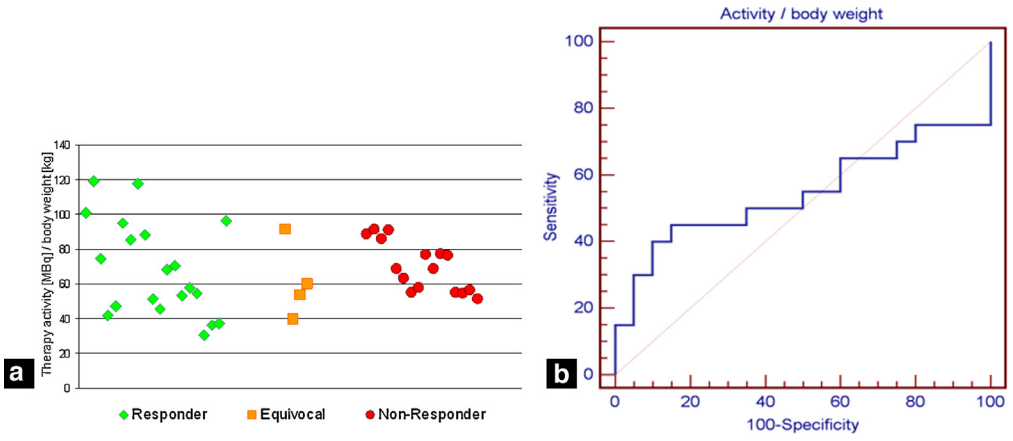

Figure 7. The applied treatment radioactivity in relation to body weight without considering specific tumor uptake measured by ^{68}Ga-DOTATOC PET/CT did not reveal any correlation with therapy response.

The primary objective of our study was to analyze retrospectively whether pre-therapeutic ^{68}Ga-DOTATOC PET/CT might be useful to identify patients with high likelihood to respond to PRRT with fixed doses of ^{90}Y-DOTATOC. Therefore, we compared the pre-therapeutic PET/CT studies of all patients scheduled for PRRT with the follow-up examination 3 months after therapy. In addition, we evaluated the clinical assessment and laboratory findings, in particular the tumor markers chromogranin A, NSE, serotonin.

Our study demonstrated that both pre-therapeutic ^{68}Ga-DOTATOC tumor uptake as well as assumed uptake of ^{90}Y-DOTATOC are strongly associated with the results of subsequent PRRT. Furthermore, we could show that prediction of therapy response might be achieved using cut-off values for ^{68}Ga-DOTATOC uptake or assumed ^{90}Y-DOTATOC uptake, i.e. SUVmax more than 17.9 or more than 1.26 MBq/g, respectively.

By using pre-therapeutic ^{68}Ga-DOTATOC uptake with SUVmax more than 17.9 as cut-off value, all responders (20/20) could be separated from the majority of non-responders (15/16); only one non-responder showed a higher tumor uptake (SUVmax 26.7). Four patients, who presented equivocal follow-up findings, i.e. increase of ^{68}Ga-DOTATOC uptake, but stable disease in morphology (CT) and clinical findings, and falling tumor markers revealed a pre-therapeutic uptake SUVmax less or equal to 17.9.

By defining a threshold of more than 1.26 MBq/g, the assumed pre-therapeutic tumor uptake of ^{90}Y-DOTATOC (applied treatment activity [MBq]/body weight [g] $\times$ SUVmax), representing a surrogate of the target dose, correctly identified 19 out of 20 responders. Only one responder revealed a lower tumor uptake (0.91 MBq/g). The majority of non-responders (14/16) was correctly classified too. Only two patients showed higher tumor uptake with 2.29 MBq/g and 1.41 MBq/g, respectively. Again the same four patients with equivocal findings in the follow-up period demonstrated pre-therapeutically an assumed ^{90}Y-DOTATOC tumor uptake well below the limit of 1.26 MBq/g.

Our results support previous data that quantitative analysis of pre- and post-therapeutic ^{68}Ga-DOTATOC PET with an increased SUV at baseline is associated with increased receptor binding, indicating a favorable therapeutic effect [44].

Interestingly, our data are in contrast to a recently published paper by Gabriel et al. [45] who stated that SUV analysis did not show a clear cut-off trend, and that there was no significant correlation with therapy outcome parameters.

Several possible explanations for this discrepancy may be urged. First of all, our patients received a single PRRT with standardized doses in contrast to an individualized therapy protocol with a variable number of treatment cycles. In our series, PRRT was the only treatment modality that was carried out between initial and follow-up examinations with the exception of somatostatin analogues, which were stopped 6 weeks before the initial and follow-up evaluation. Furthermore, there was only a little time gap of 1 day to 3 days between ^{68}Ga-DOTATOC PET/CT and somatostatin receptor radiotherapy to ensure maximum validity of uptake results.

According to our protocol, distribution of ^{68}Ga-DOTATOC was evaluated visually and semi-quantitatively. For quantitative analysis, one reference lesion was defined and assigned as target lesion for follow-up, both SUV analysis and morphological evaluation.

Another important aspect may be the different uptake times for ^{68}Ga-DOTATOC. We prefer an interval of 20 min after injection whereas Gabriel et al. reported an acquisition time between 90—100 min. In our experience, an uptake time of ^{68}Ga-DOTATOC of 20 min is adequate to obtain satisfactory images with significantly less disturbing bowel activity, thus saving examination time, improving patient comfort, and optimizing image interpretation [46].

There are also some limitations of this study. The SUV criteria were described for imaging with ^{18}F-FDG, but not for somatostatin analogues. A decrease in SUVmax can be due to tumor regression, but also due to tumor dedifferentiation with loss of somatostatin receptors. Therefore, the use of this functional criterion should be considered as a ''hypothesis'' until more studies are available supporting this approach [47].

A further potential drawback of our study is the missing systematic correlation with ^{18}F-FDG-PET. The heterogeneous nature of NET makes it challenging to find a uniformly applicable imaging procedure. It is well known that the changes in the FDG uptake correlate significantly with tumor response [48]. The main use of FDG PET in diagnosis of NET depends on the grade of differentiation and/or aggressiveness of NETs. Thus, ^{18}F-FDG-PET/CT could be helpful in predicting therapy outcome, i.e. patients with high ^{18}F-FDG uptake are less likely to respond to PRRT [49].

The tumor uptake, in fact, is a rough estimate of the subsequent absorbed dose delivered by the PRRT. Clearly the assumed ^{90}Y-DOTATOC tumor uptake constitutes a virtual value because ^{68}Ga-DOTATOC SUVmax is not directly related to ^{90}Y-DOTATOC uptake, given the differences in chemistry, kinetics and, ultimately, different receptor binding characteristics of the two compounds. Furthermore, the variable amount of peptides used may influence somatostatin receptor binding as well. Besides, tumor uptake may change over time, depending on the tissue type. Hence, the translation of ^{68}Ga-DOTATOC uptake into an estimated ^{90}Y-DOTATOC uptake is still only a hypothesis. Therefore, a thorough dosimetric study, taking into consideration the absorbed dose of the tumor deriving from ^{90}Y-DOTATOC may have rendered this study more accurate. Another interesting issue would be an analysis of the correlation of the tumor uptake with survival parameters such as progression-free survival, which should be evaluated in future studies.

On the other hand, ^{68}Ga-DOTATOC uptake is based on PET technology which is significantly more reliable than any other measurement techniques of planar scintigraphy or SPECT. However, we believe that ^{68}Ga-DOTATOC uptake may reflect the true therapy uptake to a certain extent and, therewith, it may be useful for the purpose of optimizing therapeutic options (e.g. individual dosing), and selecting patients with high probability of advantageous therapy results.

Conclusion

Pre-therapeutic ^{68}Ga-DOTATOC tumor uptake (SUVmax > 17.9) as well as assumed uptake of ^{90}Y-DOTATOC (> 1.26 MBq/g) are strongly associated with the results of

subsequent PRRT. The defined cut-off values should be confirmed by prospective studies and may then provide the rationale for individual dosing and selecting patients with high likelihood of favorable treatment outcome.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Gustafsson BI, Siddique L, Chan A, Dong M, Drozdov I, Kidd M, et al. Uncommon cancers of the small intestine, appendix and colon: an analysis of SEER 1973-2004, and current diagnosis and therapy. Int J Oncol 2008;33:1121—31.

[2] Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97(4):934—59.

[3] Hemminki K, Li X. Familial carcinoid tumors and subsequent cancers: a nation-wide epidemiologic study from Sweden. Int J Cancer 2001;94:444—8.

[4] Newton JN, Swerdlow AJ, dos Santos Silva IM, Vessey MP, Grahame-Smith DG, Primatesta P, et al. The epidemiology of carcinoid tumors in England and Scotland. Br J Cancer 1994;70:939—42.

[5] Niederle MB, Hackl M, Kaserer K, Niederle B. Gastro-entero-pancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer 2010;17(4):909—18, http://dx.doi.org/10.1677/ERC-10-0152.

[6] Noronha YS, Raza AS. Well-differentiated neuroendocrine (carcinoid) tumors of the extrahepatic biliary ducts. Arch Pathol Lab Med 2010;134:1075—9.

[7] Spigel DR, Hainsworth JD, Greco FA. Neuroendocrine carcinoma of unknown primary site. Semin Oncol 2009;36:52—9.

[8] Reubi JC, Mäcke HR, Krenning EP. Candidates for peptide receptor radiotherapy today and in the future. J Nucl Med 2005;46(Suppl.), 67S—75S.

[9] Oberg K. Somatostatin analog octreotide LAR in gastro-entero-pancreatic tumors. Expert Rev Anticancer Ther 2009;9:557—66.

[10] Ito T, Okusaka T, Nishida T, Yamao K, Igarashi H, Morizane C, et al. Phase II study of sunitinib in Japanese patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumor. Invest New Drugs 2012 [Epub ahead of print].

[11] Grozinsky-Glasberg S, Gross DJ. New drugs in the therapy of neuroendocrine tumors. J Endocrinol Invest 2012;35(10):930—6.

[12] Kulaksiz H, Eissele R, Rössler D, Schulz S, Höllt V, Cetin Y, et al. Identification of somatostatin receptor subtypes 1, 2A, 3, and 5 in neuroendocrine tumors with subtype specific antibodies. Gut 2002;50:52—60.

[13] Van Essen M, Krenning EP, De Jong M, Valkema R, Kwekkeboom DJ. Peptide Receptor Radionuclide Therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumors. Acta Oncol 2007;46:723—34.

[14] Kaltsas GA, Papadogias D, Makras P, Grossman AB. Treatment of advanced neuroendocrine tumors with radiolabelled somatostatin analogues. Endocr Relat Cancer 2005;12:683—99.

[15] Bodei L, Ferone D, Grana CM, Cremonesi M, Signore A, Dierckx RA, et al. Peptide receptor therapies in neuroendocrine tumors. J Endocrinol Invest 2009;32:360—9.

[16] Teunissen JJ, Kwekkeboom DJ, Valkema R, Krenning EP. Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr Relat Cancer 2011;18(Suppl 1):S27—51, http://dx.doi.org/10.1530/ERC-10-0282.

[17] Pfeifer AK, Gregersen T, Grønbæk H, Hansen CP, Müller-Brand J, Herskind Bruun K, et al. Peptide receptor radionuclide therapy with Y-DOTATOC and (177)Lu-DOTATOC in advanced neuroendocrine tumors: results from a Danish cohort treated in Switzerland. Neuroendocrinology 2011;93(3):189—96.

[18] Muros MA, Varsavsky M, Iglesias Rozas P, Valdivia J, Delgado JR, Forrer F, et al. Outcome of treating advanced neuroendocrine tumors with radiolabelled somatostatin analogues. Clin Transl Oncol 2009;11:48—53.

[19] Grozinsky-Glasberg S, Barak D, Fraenkel M, Walter MA, Müeller-Brand J, Eckstein J, et al. Peptide receptor radioligand therapy is an effective treatment for the long-term stabilization of malignant gastrinomas. Cancer 2011;117(7):1377—85.

[20] Forrer F, Valkema R, Kwekkeboom DJ, de Jong M, Krenning EP. Neuroendocrine tumors. Peptide receptor radionuclide therapy. Best Pract Res Clin Endocrinol Metab 2007;21:111—29.

[21] Teunissen JJ, Kwekkeboom DJ, Krenning EP. Quality of life in patients with gastroenteropancreatic tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Clin Oncol 2004;22:2724—9.

[22] Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124—30.

[23] Faiss S, Pape UF, Böhmig M, Dörffel Y, Mansmann U, Golder W, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors—the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003;21:2689—96.

[24] Kwekkeboom DJ, Teunissen JJ, Bakker WH, Kooij PP, de Herder WW, Feelders RA, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3] octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005;23:2754—62.

[25] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205—16.

[26] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228—47.

[27] O'Donoghue JA, Bardiès M, Wheldon TE. Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides. J Nucl Med 1995;36:1902—9.

[28] de Jong M, Breeman WA, Bernard BF, Bakker WH, Visser TJ, Kooij PP, et al. Tumor response after [(90)Y-DOTA(0),Tyr(3)] octreotide radionuclide therapy in a transplantable rat tumor model is dependent on tumor size. J Nucl Med 2001;42(12):1841—6.

[29] Liu SZ, Zhang YC, Mu Y, Su X, Liu JX. Thymocyte apoptosis in response to low-dose radiation. Mutat Res 1996;358:185—91.

[30] Oberg K, Jelic S, ESMO Guidelines Working Group. Neuroendocrine gastroenteropancreatic tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19(Suppl. 2):ii104—5.

[31] Al-Nahhas A, Win Z, Szyszko T, Singh A, Nanni C, Fanti S, et al. Gallium-68 PET: a new frontier in receptor cancer imaging. Anticancer Res 2007;27:4087—94.

[32] Putzer D, Kroiss A, Waitz D, Gabriel M, Traub-Weidinger T, Uprimny C, et al. Somatostatin receptor PET in neuroendocrine

tumours: 68Ga-DOTA0, Tyr3-octreotide versus 68Ga-DOTA0-lanreotide. Eur J Nucl Med Mol Imaging 2013;40(3):364—72, http://dx.doi.org/10.1007/s00259-012-2286-6.

[33] Gupta SK, Singla S, Bal C. Renal and hematological toxicity in patients of neuroendocrine tumors after peptide receptor radionuclide therapy with 177Lu-DOTATATE. Cancer Biother Radiopharm 2012;27(9):593—9.

[34] Behr TM, Goldenberg DM, Becker W. Reducing the renal uptake of radiolabeled antibody fragments and peptides for diagnosis and therapy: present status, future prospects and limitations. Eur J Nucl Med 1998;25:201—12.

[35] Rolleman EJ, Valkema R, de Jong M, Kooij PP, Krenning EP. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging 2003;30:9—15.

[36] Zhernosekov KP, Filosofov DV, Baum RP, Aschoff P, Bihl H, Razbash AA, et al. Processing of generator-produce ^{68}Ga for medical application. J Nucl Med 2007;48:1741—8.

[37] Hanley JA, McNeil BJ. Maximum attainable discrimination and the utilization of radiologic examinations. J Chronic Dis 1982;35:601—11.

[38] Krenning EP, Valkema R, Kwekkeboom DJ, de Herder WW, van Eijck CH, de Jong M, et al. Molecular imaging as in vivo molecular pathology for gastroenteropancreatic neuroendocrine tumors: implications for follow-up after therapy. J Nucl Med 2005;46(Suppl. 1), 76S—82S.

[39] Kwekkeboom DJ, Krenning EP. Radiolabeled somatostatin analog scintigraphy in oncology and immune diseases: an overview. Eur Radiol 1997;7:1103—9.

[40] Kaltsas GA, Mukherjee JJ, Isidori A, Kola B, Plowman PN, Monson JP, et al. Treatment of advanced neuroendocrine tumors using combination chemotherapy with lomustine and 5-fluorouracil. Clin Endocrinol 2002;57:169—83.

[41] Waldherr C, Pless M, Maecke HR, Schumacher T, Crazzolara A, Nitzsche EU, et al. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq 90Y-DOTATOC. J Nucl Med 2002;43:610—6.

[42] Paganelli G, Bodei L, Handkiewicz Junak D, Rocca P, Papi S, Lopera Sierra M, et al. 90Y-DOTA-D-Phe1-Try3-octreotide in therapy of neuroendocrine malignancies. Biopolymers 2002;66:393—8.

[43] Kwekkeboom DJ, Mueller-Brand J, Paganelli G, Anthony LB, Pauwels S, Kvols LK, et al. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. J Nucl Med 2005;46(Suppl. 1):62S—6S.

[44] Koukouraki S, Strauss LG, Georgoulias V, Eisenhut M, Haberkorn U, Dimitrakopoulou-Strauss A. Comparison of the pharmacokinetics of 68Ga-DOTATOC and [18F]FDG in patients with metastatic neuroendocrine tumors scheduled for 90Y-DOTATOC therapy. Eur J Nucl Med Mol Imaging 2006;33:1115—22.

[45] Gabriel M, Oberauer A, Dobrozemsky G, Decristoforo C, Putzer D, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. J Nucl Med 2009;50:1427—34.

[46] Miederer M, Seidl S, Buck A, Scheidhauer K, Wester HJ, Schwaiger M, et al. Correlation of immunohistopathological expression of somatostatin receptor 2 with standardised uptake values in 68Ga-DOTATOC PET/CT. Eur J Nucl Med Mol Imaging 2009;36:48—52.

[47] Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 2010;37(1):181—200.

[48] Baum RP, Prasad V. Monitoring treatment. In: Cook GJR, Maisey MN, Britton KE, Chengazi V, editors. Clinical nuclear medicine. 4th ed London, UK: Hodder Arnold; 2006. p. 57—78.

[49] Oh S, Prasad V, Lee DS, Baum RP. Effect of Peptide Receptor Radionuclide Therapy on somatostatin receptor status and glucose metabolism in neuroendocrine tumors: intraindividual comparison of Ga-68 DOTANOC PET/CT and F-18 FDG PET/CT. Int J Mol Imaging 2011;2011:524130, http://dx.doi.org/10.1155/2011/524130.