The Bad Berka Dose Protocol: Comparative Results of Dosimetry in Peptide Receptor Radionuclide Therapy Using ^{177}Lu-DOTATATE, ^{177}Lu-DOTANOC, and ^{177}Lu-DOTATOC

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Abstract

Purpose: The objective of this study is to analyze the in vivo behavior of the ^{177}Lu-labeled peptides DOTATATE, DOTANOC, and DOTATOC used for peptide receptor radionuclide therapy (PRRNT) of neuroendocrine tumors (NETs), by measuring organ and tumor kinetics and by performing dosimetric calculations. *Methods*: Two hundred fifty-three patients (group 1) with metastasized NET who underwent PRRNT were examined. Out of these, 185 patients received ^{177}Lu-DOTATATE, 9 were treated with ^{177}Lu-DOTANOC, and 59 with ^{177}Lu-DOTATOC. Additionally, 25 patients receiving, in consecutive PRRNT cycles, DOTATATE followed by DOTATOC (group 2) and 3 patients receiving DOTATATE and DOTANOC (group 3) were analyzed. Dosimetric calculations (according to MIRD scheme) were performed using OLINDA software. *Results*: In group 1, DOTATOC exhibited the lowest and DOTANOC the highest uptake and therefore mean absorbed dose in normal organs (whole body, kidney, and spleen). In group 2, there was a significant difference between DOTATATE and DOTATOC concerning kinetics and normal organ doses. ^{177}Lu-DOTATOC had the lowest uptake/dose delivered to normal organs and highest tumor-to-kidney ratio. There were no significant differences between the three peptides concerning tumor kinetics and mean absorbed tumor dose. *Conclusions*: The study demonstrates a

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correlation between high affinity of DOTANOC in vitro and high uptake in normal organs/whole body in vivo, resulting in a higher whole-body dose. DOTATOC exhibited the lowest uptake and dose delivered to normal tissues and the best tumor-to-kidney ratio. Due to large interpatient variability, individual dosimetry should be performed for each therapy cycle.

Keywords

PRRNT · DOTATATE · DOTATOC · DOTANOC · Affinity · Dosimetry

Contents

1   Introduction

There are few treatment options for inoperable or metastasized gastroenteropancreatic (GEP) neuroendocrine tumors (NETs). The majority of well-differentiated NETs express somatostatin receptors (SSTR) and can therefore be visualized and treated with radiolabeled somatostatin analogs (SSTA) (Rufini et al. 2006; Prasad et al. 2010). Due to encouraging clinical results, peptide receptor radionuclide therapy (PRRNT) with radiolabeled SSTA is now established as a treatment modality in advanced NETs (De Jong et al. 2002; Kwekkeboom et al. 2005a; Cremonesi et al. 2006; Otte et al. 1998).

Most NETs predominantly overexpress SSTR subtype 2. Hence, it is important to use a somatostatin analog with high affinity to SSTR2. The different subtype receptor affinity profiles of the various somatostatin analogs result in different uptake and kinetics in normal tissues and tumors. This has important therapeutic implications, since the goal of any internal radiation therapy is to deliver the maximal dose to the tumor while sparing normal organs from damage. In addition, the large variability in biodistribution and tumor uptake among individual patients must be taken into account. For this reason, accurate and individualized dosimetry

is essential to ensure maximal tumor doses while preserving normal organ function. This is especially true for the kidneys and bone marrow, which are the dose-limiting organs when performing PRRNT.

Most frequently, the radionuclides ^{90}Y and ^{177}Lu are used for PRRNT (Kwekkeboom et al. 2005a). In contrast to ^{90}Y, which is a pure β-emitter, ^{177}Lu is also a γ-emitter of low emission abundance. These characteristics enable imaging and therapy with the same compound and also allow dosimetry during treatment. The most commonly used peptides for PRRNT are DOTATOC and DOTATATE. In vitro, DOTATATE has the highest affinity to SSTR2 (Reubi et al. 2000). Labeled with ^{177}Lu, DOTATATE was shown to be successful in terms of tumor regression and survival in an animal model. Partial (and some complete) remissions were described in patients undergoing PRRNT (Kwekkeboom et al. 2005b; Erion et al. 1999). The peptide DOTANOC has the highest affinity to SSTR3 and 5, and also high affinity to SSTR2 (Wild et al. 2003). In previous studies we have shown that ^{90}Y-DOTANOC is more toxic than ^{90}Y-DOTATATE, probably because of the higher uptake in normal tissues. When comparing ^{177}Lu-DOTANOC with ^{177}Lu-DOTATATE, we again observed higher uptake of ^{177}Lu-DOTANOC in whole body and normal tissues, but no significantly higher tumor uptake and resulting tumor dose was found (Prasad et al. 2007; Wehrmann et al. 2007). Therefore, DOTANOC is no longer used for PRRNT at our center. However, for comparison with DOTATATE and DOTATOC, results obtained when using DOTANOC were also taken into consideration for the purpose of this study.

Calculating the absorbed dose is important for determination of risk and therapeutic benefit of internal radiation therapy. Because direct measurements are difficult to perform in clinical routine, the absorbed dose is calculated by measuring uptake and retention of the administered radiopharmaceutical. The MIRD scheme provides, together with measurements of the biologic distribution, a method for calculating absorbed doses of radionuclides (Siegel et al. 1999; Bolch et al. 2009). Optimal dose estimation requires time-consuming and sophisticated methods which are difficult due to practical (e.g., patient status) and physical reasons. Nevertheless, to make dosimetry available for most of the patients, we have developed a specific dosimetry procedure used in daily clinical routine (Wehrmann et al. 2007).

The aim of this study is to compare the pharmacokinetics and dosimetry of ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC, and ^{177}Lu-DOTANOC considering inter- and intrapatient variability in a large cohort of patients undergoing PRRNT.

2 Patients and Methods

2.1 Patients

All patients enrolled in this study were suffering from metastatic NETs with liver, lymph node, bone, or other organ involvement. Intense SSTR expression of (inoperable) primary tumors and metastases had been verified before therapy

Table 1 Patients treated with different peptides (group 1)

	DOTATATE	DOTANOC	DOTATOC
Therapy cycles	185	9	59
	83 male, 102 female	3 male, 6 female	35 male, 24 female
	59.7 ± 10.6 years	64.4 ± 9.9 years	62.3 ± 10.0 years
	27.5–79.7 years	47.9–77.5 years	41.2–81.7 years
Activity per cycle in GBq	5.7 ± 1.1	5.6 ± 1.5	7.3 ± 0.8
	2.5–8.5	3.6–7.4	5.5–8.6

Table 2 Patients treated with DOTATATE and DOTATOC (group 2)

	DOTATATE	DOTATOC
25 patients; 13 male, 12 female	60.2 ± 9.1 years	61.7 ± 9.1 years
	45.3–75.2 years	45.6–75.5
Activity per cycle (GBq)	6.5 ± 1.1	7.3 ± 0.7
	5.0–9.5	5.5–8.5

by using ^{68}Ga-DOTANOC, ^{68}Ga-DOTATOC, or ^{68}Ga-DOTATATE PET/CT. Before PRRNT, each patient was extensively informed about the therapeutic procedure and possible adverse effects. All patients provided written informed consent to undergo treatment and follow-up. The study was approved by the local Ethics Committee and performed in accordance with German regulations concerning radiation safety. Three groups of patients receiving PRRNT were included in this study. The first group consisted of 253 patients (group 1, Table 1), treated with 1–6 cycles of ^{177}Lu-labeled DOTATATE, DOTANOC, or DOTATOC. Differences with respect to kinetics, biodistribution, and mean absorbed doses between the three different peptides were analyzed on the basis of dosimetric data obtained in this group (interindividual comparison). Group 2 consisted of 25 patients (Table 2) who received PRRNT first using ^{177}Lu-DOTATATE and in a following cycle using ^{177}Lu-DOTATOC, to compare kinetics and mean absorbed dose in the same patient (intraindividual variability). The mean time between these therapy courses was 18 months. In case of more than one cycle with each peptide, two consecutive cycles were chosen for dosimetric analyses. Additionally, kinetics and biodistribution were analyzed in three patients (group 3) treated using both ^{177}Lu-DOTANOC and ^{177}Lu-DOTATATE, to assess the intrapatient variability when using these two peptides. The administered activity was 4.5, 4, and 4.2 GBq ^{177}Lu-DOTANOC and 6.5, 4.3, and 4.8 GBq of ^{177}Lu-DOTATATE, respectively.

2.2 Radiopharmaceuticals

The radiopharmaceuticals were prepared in our GMP-certified radiopharmacy. ^{177}Lu-labeling of DOTA peptides was performed according to the following procedure: A solution of 500 μg 2,5-dihydroxybenzoic acid and 20 μg of the corresponding DOTA peptide in 50 μL 0.4 M sodium acetate buffer (pH 5.5) was added to a solution of 1 GBq ^{177}Lu in 30 μL 0.05 M HCl. The mixture was heated to 90°C for 30 min and then diluted with 0.9% saline solution followed by sterile filtration. Quality control was performed by RP-18 HPLC [solvent A: water; solvent B: acetonitrile (both with 0.1% TFA); 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.

2.3 Infusion and Renal Protection

For kidney protection, every patient was infused with 1500 mL of a renoprotective amino acid mixture of 5% lysine HCl and 10% L-arginine HCl. Infusion was started 30 min prior to administration of the therapeutic dose and continued for 4 h thereafter. This co-infusion of amino acids reduces renal exposure significantly (Jamar et al. 2003). The radiopharmaceutical was co-administered over 10–15 min by using a second infusion pump system. The activity to administer was individually chosen based on the uptake in the tumor lesions as shown by Ga-68 SSTR PET/CT (performed before each treatment cycle), kidney function (tubular extraction rate determined by Tc-99m MAG3 scintigraphy and glomerular filtration by Tc-99m DTPA clearance, and serum creatinine), hematological reserve, previous treatments, general status of the patient (Karnofsky Performance Scale), and experience reported by other groups (Kwekkeboom et al. 2005a).

2.4 Dosimetry

In this study, the dosimetric approach is based on the MIRD scheme, where the absorbed dose depends on two main parameters:

1. Time-independent physical factors: so-called S-values, which were tabulated by the MIRD committee and include type, size of emitted energies, and geometric aspects (size, type, and structure of source and target regions);
2. Time-dependent biokinetic factors: these describe the cumulated activity, uptake, and retention in the regions of interest, and include the physical half-life of the radionuclide and the biologic half-life of the radiopharmaceutical (expressed as residence time, which also depends on the half-life of the radionuclide and its distribution) (Siegel et al. 1999).

The dose estimation requires an accurate determination of the time-dependent activity of the source regions. Thus, the main objective of the dosimetry is correct evaluation of the distribution and kinetics of the administered radiopharmaceutical

(Sgouros 2005; Stabin and Siegel 2003). For the dose estimations, we developed a convenient procedure which is based on the MIRD scheme and practicable in daily clinical routine (Wehrmann et al. 2007). In short, the kinetics of the radiopharmaceutical is determined on the basis of five planar whole-body scintigraphies in defined time order after administration of the radiopeptide (p.i.). After the first scan acquired immediately after infusion, further scans are obtained at 3, 20, 44, and 68 h p.i. The camera parameters were the following: MEDISO spirit DH-V dual-headed gamma camera, MeGP collimator, 15% energy window, peak at 208 keV, speed 15 cm/min. Scintigraphies were analyzed by the use of regions of interest (ROI). After geometric mean and background correction, time-dependent time–activity curves were obtained and fitted to mono- or biexponential functions (software ORIGIN PRO 8.1G). The residence time and cumulated activity as well as the uptake and effective half-life were then calculated, and the mean absorbed doses were estimated by using the OLINDA/EXM software (Stabin et al. 2005).

Finally, uptake values were calculated as fraction of administered activity (%IA), and effective half-lives, residence times, and mean absorbed organ and tumor doses were obtained for whole body, normal tissues, kidneys, spleen, and tumor lesions of all patients in the different groups. The ROIs for normal tissue and background were placed over those regions showing no tumor involvement. For interpatient comparison, they were scaled to 10% of the whole-body ROI. Estimation of mean absorbed tumor dose requires the lesions' volume. These were obtained from the CT data of the pretherapy ^{68}Ga-DOTA-SSTR PET/CT. Volumes of normal organs were assumed to have standard size as given by OLINDA/EXM.

Organs showing tumor involvement or overlaying with other source regions were not included for dosimetric analysis. For this reason, normal liver was excluded from the analysis in this study because nearly all patients had extensive liver metastases. Some patients had liver lesions superimposing on the right kidney, allowing only analysis of the left kidney. In these cases, it was assumed that the mean absorbed dose would be identical for both kidneys (which was also checked and confirmed by prior Tc-99m MAG3 scintigraphy proving that there was no significant difference in the differential renal function). Also, kinetics and mean absorbed dose of the spleen could not be estimated for all patients as several patients had undergone splenectomy.

2.5   Comparison and Statistics

Dosimetric parameters were determined for whole body, kidneys, spleen, and normal tissues/organs as well as for tumor lesions. Results are expressed as median values. To describe differences between the various radiolabeled peptides, the following parameters were chosen: uptake at 20 h p.i. (max. uptake for tumor lesions), half-life, residence time, and mean absorbed dose. Interpatient variability was estimated by comparing the three peptides in all patients. To describe significant differences among the peptides, nonparametric tests for independent samples were used. In group 2, statistically significant differences were evaluated by nonparametric signed-rank tests for paired samples. All statistical tests were

performed using ORIGINPRO 8.1 G; p-values ≤ 0.05 were considered to be significant.

3 Results

3.1 Normal Organs

Dosimetry results are given in Table 3; corresponding uptake and time–activity curves are shown in Fig. 1.

3.1.1 Whole Body

Because the total whole-body counts from the first scan represent the total administered activity, whole-body kinetics start with an initial uptake of 100% for all three peptides. Initially, the curves show a rapid decline followed by a second, slower decline. Therefore, time–activity curves for whole body were fitted by a biexponential function. The highest initial whole-body (WB) uptake was observed for DOTANOC and the lowest for DOTATOC. At 20 h p.i., WB uptake was again highest for DOTANOC, followed by DOTATATE and DOTATOC, correlating with the first half-life, which was shorter for DOTATATE and DOTATOC as compared with DOTANOC. Similar results were calculated regarding the second half-life: DOTANOC exhibited the longest WB residence time, while DOTATOC had the fastest washout. The estimated whole-body dose was therefore highest with DOTANOC, followed by DOTATATE and DOTATOC. There were significant differences in all parameters, when comparing DOTATATE with DOTATOC (Table 4). Except for the second half-life, parameters were also significantly different between DOTATATE and DOTANOC. When comparing DOTANOC with DOTATOC, there were significant differences with respect to uptake, residence time, and mean absorbed dose. The following results were obtained in the 25 patients receiving DOTATATE and DOTATOC: 24 out of the 25 patients (96%) exhibited higher WB uptake for DOTATATE as compared with DOTATOC at 20 h p.i. First half-life was longer for DOTATOC in 22 patients (88%) whereas for DOTATATE second half-life was longer in 17 (68%), and residence time in 23 patients (92%). In 22 patients (88%) whole-body dose was slightly, but statistically significantly, higher when using DOTATATE as compared with DOTATOC. In group 3, i.e., patients treated with DOTATATE and DOTANOC, the following results were obtained: in two out of three patients, DOTANOC had higher uptake at 20 h p.i., and longer first half-life and residence time. One patient also showed longer second half-life and higher mean absorbed WB dose when using DOTANOC.

3.1.2 Normal Tissues

Comparable results were obtained for whole-body kinetics and normal tissues. DOTATOC showed the lowest uptake and DOTANOC the highest uptake, with the exception of the values directly after injection and 3 h p.i. First half-life of the

Table 3 Dosimetric results of 253 patients in group 1 (median and range of variation); for kidneys, spleen, and tumor lesions only the second half-life was calculated because of the fit to a monoexponential function

|	DOTA-	Whole body	Normal tissue	Kidneys	Spleen	Tumor lesions
Uptake 20 h p.i.	TATE	27.7 (14.1–58.7)	1.8 (0.9–5.1)	2.4 (0.9–6.7)	1.7 (0.4–14.3)	0.05 (0.001–0.8)
	NOC	38.5 (22.6–70.1)	2.7 (1.9–5.3)	3.2 (2.2–3.6)	1.6 (1.0–4.8)	0.02 (0.004–0.3)
	TOC	19.5 (10.2–52.2)	1.4 (0.7–3.6)	1.6 (0.7–3.3)	1.0 (0.3–4.6)	0.04 (0.001–0.4)
First half-life (h)	TATE	2.2 (0.9–6.8)	2.2 (1.0–8.4)	–	–	–
	NOC	3.0 (0.8–4.2)	2.6 (1.6–3.9)	–	–	–
	TOC	2.7 (1.4–5.9)	2.8 (1.7–8.6)	–	–	–
Second half-life (h)	TATE	55.3 (33.1–94.5)	46.6 (32.4–160.3)	62.7 (36.0–160.3)	67.5 (42.9–160.3)	73.2 (31.1–160.3)
	NOC	57.3 (40.2–69.1)	43.4 (36.4–47.7)	70.3 (49.7–94.1)	79.3 (69.4–101.6)	61.2 (40.5–139.8)
	TOC	51.1 (30.3–82.4)	43.1 (20.1–160.3)	63.4 (37.7–142.0)	72.5 (45.8–160.3)	79.0 (31.1–160.3)
Residence time (h)	TATE	32.2 (17.7–78.6)	2.2 (1.1–7.8)	2.7 (1.0–8.3)	2.1 (0.5–16.1)	0.7 (0.02–54.7)
	NOC	50.0 (22.8–73.0)	2.9 (2.0–5.5)	3.8 (2.0–4.6)	2.3 (1.1–7.1)	0.8 (0.01–34.0)
	TOC	23.3 (14.6–66.2)	1.8 (1.2–4.4)	1.9 (0.9–5.0)	1.3 (0.3–5.9)	0.4 (0.03–36.8)
Absorbed dose (mGy/MBq)	TATE	0.05 (0.02–0.1)	–	0.8 (0.3–2.6)	1.1 (0.2–9.3)	5.2 (0.1–89.6)
	NOC	0.07 (0.04–0.1)	–	1.1 (0.6–1.5)	1.3 (0.7–3.4)	2.0 (0.5–31.7)
	TOC	0.03 (0.02–0.08)	–	0.6 (0.3–1.6)	0.7 (0.2–2.8)	4.9 (0.3–39.7)
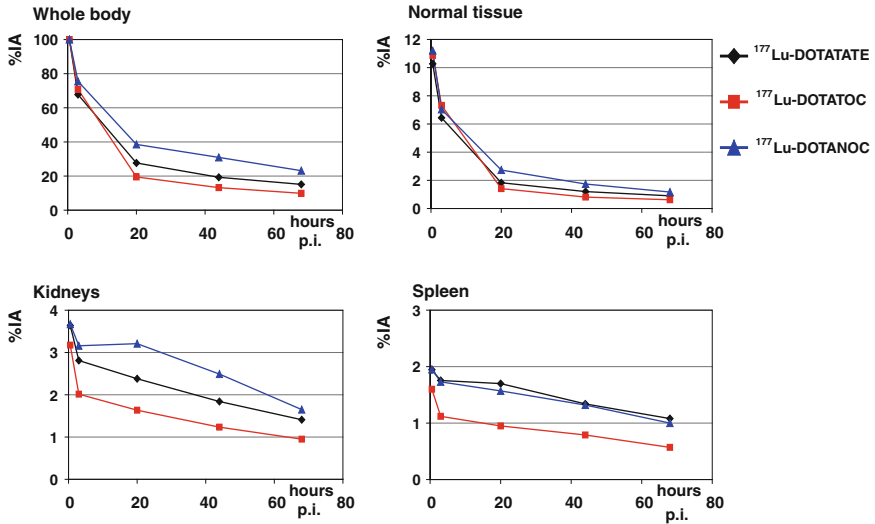
Fig. 1 Kinetics of normal organs and whole body in patients treated with different peptides (group 1)

Table 4 Significant differences between patients (group 1) treated with different peptides (indicated for respective pairs of peptides by •)

	Whole body					Normal tissue				Kidneys				Spleen			
	Up	HL1	HL2	RT	Dose	Up	HL1	HL2	RT	Up	HL	RT	Dose	Up	HL	RT	Dose
TATE–TOC	•	•	•	•	•	•	•	•	•	•		•	•	•	•	•	•
TATE–NOC	•	•		•	•	•		•	•						•		
NOC–TOC	•			•	•	•			•	•	•	•	•		•	

Up uptake, *HL1* first half-life, *HL2* second half-life

biexponential curve was longest for DOTATOC, followed by DOTANOC and DOTATATE. Otherwise, the second half-life was almost similar for DOTATOC and DOTANOC in contrast to the longer second half-life of DOTATATE. The shortest residence time was calculated for DOTATOC followed by DOTATATE and DOTANOC, which exhibited the longest residence time. As shown in Table 4 and similar to the results for whole body, all parameters were significantly different when comparing DOTATATE and DOTATOC. Except for the first half-life, the results were significantly different for DOTATATE versus DOTANOC; however, for DOTANOC versus DOTATOC only uptake at 20 h p.i. and residence time were found to be significantly different. Results in group 2 were comparable: 24 out of 25 patients had higher WB uptake at 20 h p.i. when injected with

DOTATATE; second half-life and residence time were longer in 16 (64%) and 22 (88%) patients, respectively. However, first half-life was longer for DOTATOC in 21 patients. For normal tissues, all differences between DOTATATE and DOTATOC in the same patient were statistically significant. Higher values were found for uptake, first half-life, and residence for DOTANOC in two out of three patients when comparing DOTANOC and DOTATATE in the same patient.

3.1.3 Kidneys

The kidneys are the dose-limiting organs for PRRNT. Kidneys were analyzed in 171 patients having undergone treatment with DOTATATE, in 7 treated with DOTANOC, and in 58 patients receiving PRRNT with DOTATOC. Renal uptake was highest for DOTANOC and lowest for DOTATOC. For all three peptides, renal uptake showed a rapid decline between the first scan and 3 h p.i. From 20 h p.i. the curves were fitted to a monoexponential function, with the longest half-life for DOTANOC and the shortest for DOTATATE. Similarly, residence time was longest for DOTANOC and shortest for DOTATOC. Therefore, the highest renal dose was calculated when using DOTANOC for PRRNT, followed by DOTA-TATE and DOTATOC. Direct comparison between DOTATATE and DOTANOC revealed no significant differences. For DOTATOC versus DOTATATE and DOTANOC, significant differences were found for uptake, residence time, and mean absorbed renal dose. In group 2 (analysis in 22/25 patients), higher values were observed for DOTATATE in 19 of 22 patients (86%) for uptake, residence time, and mean absorbed renal dose. These results were also statistically significant. Half-life was found to be similar for both peptides (Table 2). In group 3, only two out of three patients could be evaluated because of superimposition of the liver lesions on the kidney: One patient had higher values for DOTANOC concerning uptake, half-life, residence time, and renal dose. The second patient was found to have higher uptake for DOTANOC, whereas half-life, residence time, and renal dose were higher for DOTATATE.

3.1.4 Spleen

Dosimetric parameters for the spleen were calculated in 132 patients who underwent therapy with DOTATATE, in 7 patients using DOTANOC, and in 49 patients treated with DOTATOC. In contrast to other normal organs, spleen uptake was almost similar for DOTATATE and DOTANOC. The lowest uptake was found for DOTATOC. After an initial decrease between the first two scans, the uptake of all three peptides showed a slight decrease and followed a monoexponential function 20 h p.i. The corresponding half-life was the longest for DOTANOC, followed by DOTATOC and DOTATATE. The resulting residence time was longest for DOTANOC and shortest for DOTATOC. Consequently, the highest dose to the spleen was calculated for DOTANOC and the lowest for DOTATOC. Half-life of DOTATATE and DOTANOC were significantly different. Comparing DOTANOC and DOTATOC, significant differences were found for uptake, residence time, and dose. For DOTATOC versus DOTATATE, the results were similar for whole body and normal tissue (Table 4). In group 2, the spleen dose was calculated in 17/25
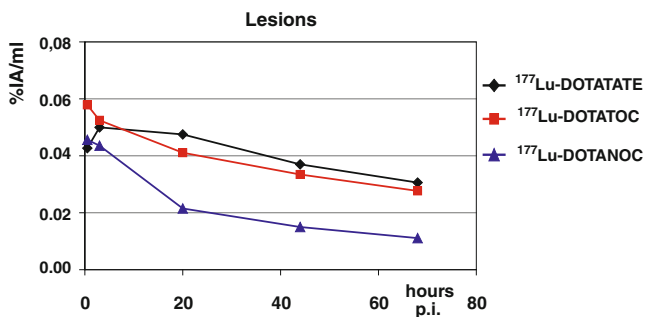
Fig. 2 Kinetics of tumor lesions in patients treated with different peptides (group 1)

patients. In 14 (82%), significantly higher uptake, longer residence time, and higher dose were observed for DOTATATE. In 13 (76%) patients, half-life was significantly longer for DOTATOC. In group 3, the comparison between DOTANOC and DOTATATE showed higher values for uptake, half-life, residence time, and mean absorbed dose for DOTANOC in one of the three patients, whereas the other two patients showed higher values for DOTATATE.

3.2 Tumor Lesions

For better comparison, uptake in tumor lesions is presented as percent of injected activity per unit volume (%IA/mL). This relation allows for comparison of tumor lesions among different peptides, because the volume dependency is eliminated. Additionally, all values are expressed as median values.

Tumor kinetics is shown in Fig. 2. In contrast to the kinetics in normal organs, DOTATATE revealed the highest uptake at 20 h p.i. DOTATOC had the highest initial uptake followed by a fast decline. Initial uptake of DOTATATE and DOTANOC were almost similar, but the retention thereafter was different. While the uptake of DOTATATE increased between the first two scans, a fast decline was found for DOTANOC. All time–activity curves were fitted by monoexponential functions from 20 h p.i. resulting in the longest half-life for DOTATOC and the shortest for DOTANOC. The longest median residence time was determined for DOTANOC and the shortest for DOTATOC. Thus, the resulting absorbed lesion doses were the highest for DOTATATE, followed by DOTATOC and DOTANOC. The differences in uptake and mean absorbed dose were not statistically significant. Only half-life and residence times of DOTATATE as compared with DOTATOC were significantly different as well as the half-life of DOTANOC versus DOTATOC. In patients from group 2, 46 tumor lesions were analyzed: 39 (85%) showed higher uptake at 20 h p.i. and 40 (87%) patients showed longer residence time for DOTATATE, while the tumor lesions of 23 (50%) patients showed longer half-life for DOTATATE. The mean absorbed dose to lesions was higher for DOTATATE in 30 patients (65%). These results are
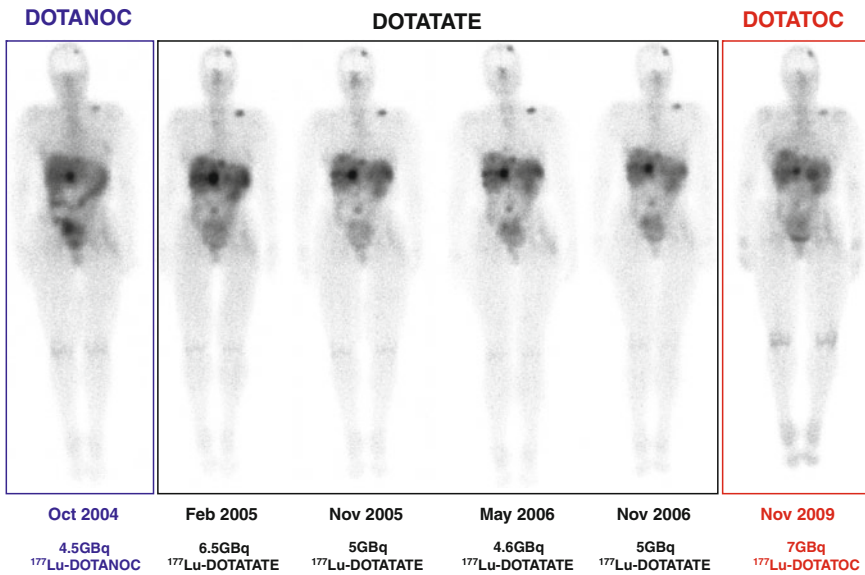
Fig. 3 Anterior whole-body scans at 20 h p.i. during six cycles of PRRNT in one patient (scaled to the maximum pixel of all scans)

statistically significant for uptake, residence time, and mean absorbed dose, but not concerning half-life.

3.3 Tumor-to-Kidney Ratio

The ratio for the three different peptides in patients from group 1 revealed the following results: DOTATOC showed the highest ratio (12), followed by DOTATATE (10) and DOTANOC (6). In patients who underwent therapy using DOTATATE and later DOTATOC (group 2), the ratio was higher for DOTATOC in 23 of 43 (53%) lesions, which was not statistically significant. Therefore, the tumor-to-kidney ratio in patients from group 2 was comparable for both peptides. Concerning group 3, the tumor-to-kidney ratio was calculated in two out of three patients: both exhibited a higher ratio for DOTANOC as compared with DOTATATE.

3.4 Variability

The data shown in Table 3 and the dosimetric results of patients in group 2 reveal high variability among patients. Moreover, high intrapatient variability was observed for patients receiving more than one cycle of therapy (data not shown). Figures 3 and 4 demonstrate the whole-body scans and the kinetics in a patient who received six cycles of therapy using all three peptides. The highest whole-body
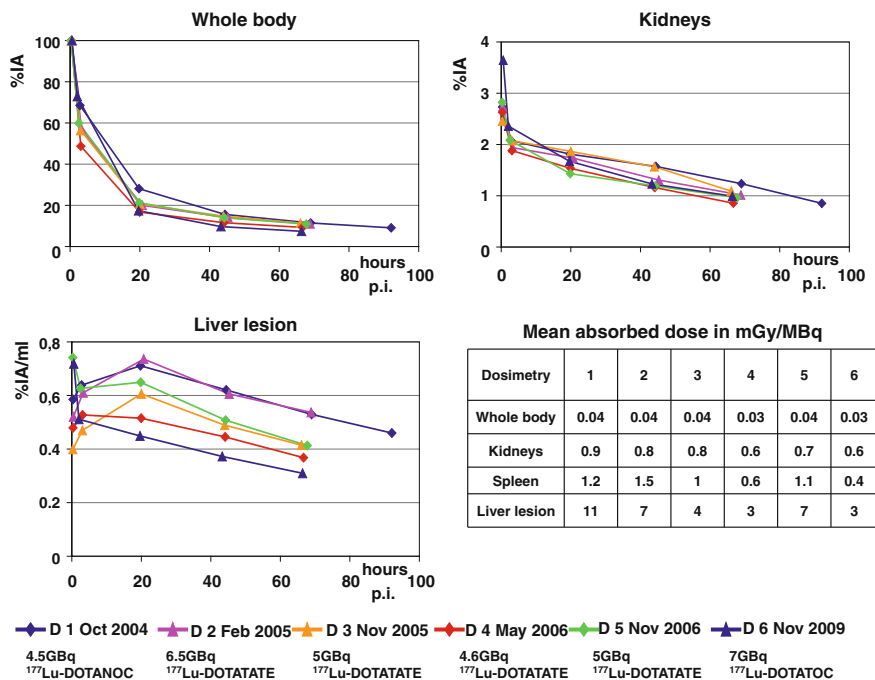
Fig. 4 Dosimetric results of six cycles of PRRNT in one patient using three different peptides

uptake was observed during the first therapy cycle when using DOTANOC, while the highest renal uptake was found during the third cycle. For the liver lesions, maximum uptake was observed during the first two therapies. DOTATOC revealed the lowest whole-body uptake. Also noticeable were the differences in the initial renal uptake; similar trend is seen for the liver lesions and the spleen (data not shown). There was no systematic pattern of uptake or mean absorbed dose in consecutive therapies.

4   Discussion

This study reports results of dosimetric analyses obtained after PRRNT of NETs. All three peptides, ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC, and ^{177}Lu-DOTANOC, showed high specific uptake in somatostatin receptor-positive tumors. Significant differences were found for all calculated parameters (uptake, half-life, residence time, and mean absorbed dose) concerning whole body, normal tissue, kidneys, and spleen for DOTATATE and DOTATOC in 25 patients receiving both peptides (group 2); similar results were obtained for all parameters in normal organs on comparison of DOTATATE and DOTATOC in different patients (group 1): uptake and mean absorbed doses were lowest for DOTATOC. The dose to whole body, spleen, and kidneys was highest for DOTANOC.

In patients who underwent treatment using DOTATATE and DOTANOC (group 3), uptake, half-life, and residence time for whole body and normal tissue, as well as the whole-body dose, were higher with DOTANOC. The preclinical studies by Wild et al. comparing ^{111}In-DOTANOC and ^{111}In-DOTATOC showed that DOTANOC had higher affinity to SSTR2, 3, and 5 (Wild et al. 2003). DOTANOC has in fact the highest affinity to SSTR3 and 5, which would imply higher uptake in normal organs or whole body in vivo and therefore higher whole-body dose, as was also demonstrated in a previous study comparing DOTATATE and DOTANOC (Wehrmann et al. 2007).

In patients treated with all three peptides, the second half-life of each peptide was longer for the spleen in contrast to the kidneys. Together with the higher renal uptake and despite the shorter half-life, a longer residence time for the kidneys was calculated. However, the highest mean absorbed doses were obtained for the spleen (1.4–39.9 Gy) as compared with whole body and kidneys. The range of the estimated mean dose to the kidney in this study was 1.5–18.2 Gy, as compared with the study by Valkema et al., who reported a renal dose of 1.8–7.8 Gy (Valkema et al. 2005). The large variability in our study could be due to a different patient population (including patients with impaired renal function). However, in comparison with ^{90}Y-labeled peptides (DOTATATE/-TOC), the renal dose with ^{177}Lu was significantly lower, which translates into lower renal toxicity (Forrer et al. 2004; Bodei et al. 2003; Helisch et al. 2004).

The mean absorbed kidney dose was significantly higher for DOTATATE as compared with DOTATOC in patient groups 1 and 2. Additionally, when comparing DOTANOC and DOTATOC among different patients, DOTATOC had a significantly lower renal dose. Since the kidney is the dose-limiting organ in PRRNT, the safe therapeutic window would be best determined by the tumor-to-kidney ratio for the absorbed doses. In this study, this ratio was comparable for DOTATATE and DOTATOC when individual lesions were considered (group 2). Forrer et al. (2004) also found a significant difference between the mean values for the two peptides.

There was no statistically significant difference concerning uptake and mean absorbed dose of tumor lesions when comparing the three peptides in group 1, i.e., in different patients. Even though a significant difference could not be demonstrated, the mean absorbed tumor dose was the highest for DOTATATE and lowest for DOTANOC. This finding is consistent with a previous study comparing ^{177}Lu-DOTATATE and ^{177}Lu-DOTANOC, in which the difference could not be statistically proven (Wehrmann et al. 2007). In patients receiving DOTATATE and DOTATOC (group 2), there was a significant difference in mean absorbed tumor dose between ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC. This is consistent with the results of Esser et al. (2006) in a study performed in seven patients.

In a preclinical study comparing the effects of ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC in nude mice xenografted with human midgut carcinoid tumor cell line (GOT1), Swärd et al. (2008) had also demonstrated a significantly higher mean absorbed dose to the tumor by using DOTATATE. Forrer et al. (2004), however, in a comparison between ^{111}In-DOTATOC and ^{111}In-DOTATATE in five patients
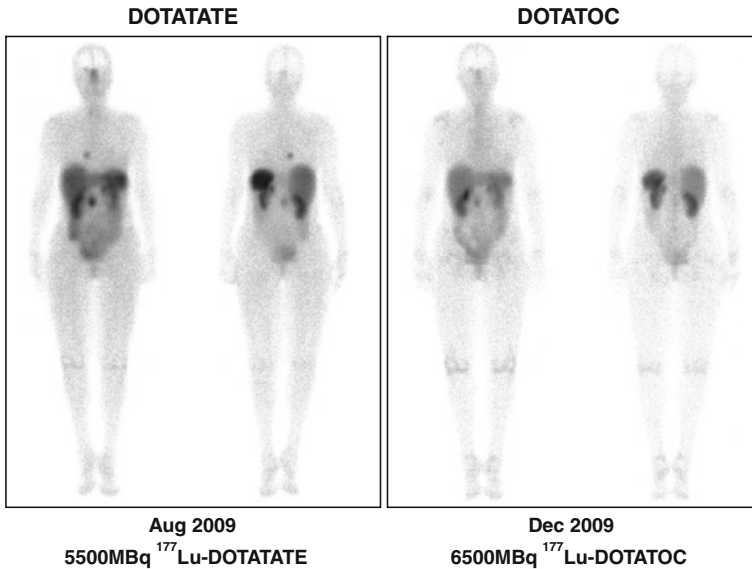
Fig. 5 Whole-body scans at 20 h p.i. in a patient treated with ^{177}Lu-DOTATATE and ^{177}Lu-DOTATOC (scaled to the maximum pixel of both scans)

with metastasized NETs, did not find a significant difference in the doses delivered. Interestingly, they found a higher mean tumor dose with ^{111}In-DOTATOC as compared with ^{111}In-DOTATATE, which is surprising since DOTATATE among all the peptides has the highest affinity to SSTR2. Kwekkeboom et al. found 3–4-fold higher uptake with ^{177}Lu-DOTATATE in comparison with ^{111}In-DTPA[0]–octreotide. This is in agreement with the higher uptake of DOTATATE found in our study and could explain the higher mean absorbed dose delivered by DOTATATE to the tumor lesions (Kwekkeboom et al. 2001); for example, Fig. 5 shows whole-body scans from a patient (group 2) who was treated using ^{177}Lu-DOTATATE and DOTATOC. The whole-body and organ uptake, as well as the uptake in the tumor lesions, is obviously lower for DOTATOC.

Furthermore, there were significant differences concerning half-life and residence time when comparing DOTATATE and DOTATOC, and for half-life when comparing DOTANOC and DOTATOC (group 1). In patients treated with DOTATATE and DOTATOC (group 2), significantly longer tumor residence time was noted for DOTATATE, which explains the higher mean absorbed tumor dose delivered. Esser et al. also found significantly longer tumor residence time for DOTATATE as compared with DOTATOC and consequently concluded that it should be the preferred peptide for PRRNT. Their results in seven patients were comparable to our findings in a larger group of patients, confirming also the accuracy of our methodology as compared with the results published in the literature (Esser et al. 2006).

High interpatient variability was found for the mean absorbed doses. This is not unexpected, since this was a heterogeneous group of patients having varying receptor densities and tumor burden. In addition, the results showed high intra-patient variability in the same patients undergoing therapy with different peptides. As this is true even for a larger group of 253 patients studied, it leads to the conclusion that the median value of a dosimetric parameter is not representative for different patients or different therapy cycles in the same patient. This variability could be well appreciated in one patient who underwent PRRNT with all three peptides (Fig. 4). Although the variability may be attributed to the difference in the biological behavior of the peptides, the fact that there might also have been an influence of previous radiopeptide therapies or other treatment modalities must be taken into account. The possible effects of previous treatments on the outcome of the current PRRNT (e.g., effect on tumor radiosensitivity) are well known from the literature (Koral and Kaminski 2003; Sgouros et al. 2003).

Moreover, the results obtained for one patient treated with six cycles of PRRNT using different peptides showed variable kinetics and mean absorbed doses, for which no ascending or descending order for consecutive therapies was found. This effect was also seen in patients who received more than one cycle of therapy using ^{177}Lu-DOTATATE (data not shown). Consequently, dosimetry for one cycle of PRRNT should not be used alone to predict the outcome of future following cycles, even if the same peptide is used.

5   Conclusions

Comparing the somatostatin analogs DOTATATE, DOTANOC, and DOTATOC radiolabeled with ^{177}Lu, the following conclusions can be drawn from this study:

- The in vitro higher affinity of DOTANOC correlates with the in vivo higher uptake for whole body and normal tissue, which results in a higher whole-body dose. Therefore, this peptide is not ideal for PRRNT.
- Concerning kidney uptake and mean absorbed dose to normal organs and whole body, DOTATOC revealed the highest tumor-to-kidney ratio and is very appropriate for PRRNT.
- DOTATATE was shown to deliver the highest tumor dose (due to the longer residence time in the malignant lesions) and is also very suitable.

Additionally, the finding of large variability should be addressed in further studies. It is recommended that median values of absorbed doses among patients should not be the only criterion used to plan PRRNT. Beside the described methods for individual dosimetry, interindividual differences should be taken into account, particularly organ functionality, metabolism, or receptor density in organs and tumor lesions.

The results of this study demonstrate further that calculation of mean absorbed doses to critical organs and tumor lesions should be considered for estimation of possible toxicity from PRRNT. In conclusion, individual dosimetry is essential for optimal PRRNT.

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