Preliminary data on biodistribution and dosimetry for therapy planning of somatostatin receptor positive tumours: comparison of ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide

Gregor J. Förster[1], Martin Engelbach[2], Jörg Brockmann[3], Helmut Reber[1], Hans-Georg Buchholz[1], Helmut R. Mäcke[4], Frank Rösch[3], Hans Herzog[5], Peter Bartenstein[1]

[1] Department of Nuclear Medicine, University Hospital Mainz, Langenbeckstrasse 1, 55101 Mainz, Germany
[2] Department of Endocrinology and Metabolism, University Hospital Mainz, Germany
[3] Institute of Nuclear Chemistry, University of Mainz, Germany
[4] Institute of Nuclear Medicine, Division of Radiological Chemistry, University of Basel, Switzerland
[5] Institute of Medicine, Research Centre Jülich, Germany

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Abstract. The somatostatin analogue ^{90}Y-DOTATOC (yttrium-90 DOTA-D-Phe[1]-Tyr[3]-octreotide) is used for treatment of patients with neuroendocrine tumours. Accurate pretherapeutic dosimetry would allow for individual planning of the optimal therapeutic strategy. In this study, the biodistribution and resulting dosimetric calculation for therapeutic exposure of critical organs and tumour masses based on the positron emission tomography (PET) tracer ^{86}Y-DOTATOC, which is chemically identical to the therapeutic agent, were compared with results based on the tracer commonly used for somatostatin receptor scintigraphy, ^{111}In-DTPA-octreotide (indium-111 DTPA-D-Phe[1]-octreotide, OctreoScan). Three patients with metastatic carcinoid tumours were investigated. Dynamic and static PET studies with 77–186 MBq ^{86}Y-DOTATOC were performed up to 48 h after injection. Serum and urinary activity were measured simultaneously. Within 1 week, but not sooner than 5 days, patients were re-investigated by conventional scintigraphy with ^{111}In-DTPA-octreotide (110–187 MBq) using an equivalent protocol. Based on the regional tissue uptake kinetics, residence times were calculated and doses for potential therapy with ^{90}Y-DOTATOC were estimated. Serum kinetics and urinary excretion of both tracers showed no relevant differences. Estimated liver doses were similar for both tracers. Dose estimation for organs with the highest level of radiation exposure, the kidneys and spleen, showed differences of 10.5%–20.1% depending on the tracer. The largest discrepancies in dose estimation, ranging from 23.1% to 85.9%, were found in tumour masses. Furthermore, there was a wide inter-subject variability in the organ kinetics. Residence times (τ_{organs}) for ^{90}Y-DOTATOC therapy were: τ_{liver} 1.59–2.79 h; τ_{spleen} 0.07–1.68 h; and $\tau_{kidneys}$ 0.55–2.46 h (based on ^{86}Y-DOTATOC). These data suggest that dosimetry based on ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide yields similar organ doses, whereas there are relevant differences in estimated tumour doses. Individual pretherapeutic dosimetry for ^{90}Y-DOTATOC therapy appears necessary considering the large differences in organ doses between individual patients. If possible, the dosimetry should be performed with the chemically identical tracer ^{86}Y-DOTATOC.

Keywords: Dosimetry – ^{86}Y-DOTATOC – ^{111}In-DTPA-octreotide – Peptide receptor radionuclide therapy – Somatostatin receptor scintigraphy

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Introduction

The radiopharmaceutical ^{111}In-DTPA-octreotide (indium-111 DTPA-D-Phe[1]-octreotide) is a somatostatin analogue which binds to somatostatin receptors with high affinity. It is widely used for scintigraphic imaging of somatostatin receptor-positive lesions, especially neuro-endocrine tumours such as carcinoids [1]. A new application is the use of labelled octreotide for peptide receptor radionuclide therapy [2, 3]. Promising results have been reported with the somatostatin analogue Tyr[3]-octreotide, which was derivatised with the chelator DOTA, enabling stable radiolabelling with the high-energy β^- particle-emitting

Gregor J. Förster (✉)
Department of Nuclear Medicine, University Hospital Mainz,
Langenbeckstrasse 1, 55101 Mainz, Germany
e-mail: foerster@nuklear.klinik.uni-mainz.de
Tel.: +49-6131-172984, Fax: +49-6131-172386

isotope yttrium-90 (^{90}Y-DOTA-D-Phe^{1}-Tyr^{3}-octreotide; ^{90}Y-DOTATOC) [2, 3, 4]. For prediction of the in vivo behaviour of ^{90}Y-DOTATOC in therapy trials, scintigraphic studies with ^{111}In-DOTATOC were performed. However, it is known that differences exist in the biodistribution of ^{111}In- and ^{90}Y-labelled tracers that are otherwise chemically analogous [5]. Since the pure β^- emitter ^{90}Y is not suitable for quantitative imaging, DOTATOC labelled with the positron-emitting isotope yttrium-86 ($T_{1/2}$ =14.74 h, 33% β^+), which is therefore chemically identical to ^{90}Y-DOTATOC, can be considered the most appropriate agent to predict the pharmacokinetics of ^{90}Y-DOTATOC [6, 7].

The aim of this study was to compare the in vivo pharmacokinetics and biodistribution of ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide in the same patients in order to obtain results which would allow assessment of the accuracy of the commonly used ^{111}In-DTPA-octreotide based dosimetry.

Materials and methods

Patients. In three patients (males aged 46–67 years), scintigraphy with ^{111}In-DTPA-octreotide and a PET investigation with ^{86}Y-DOTATOC were performed within an interval of 1 week. Medication with somatostatin analogues (octreotide, LAR, Novartis, Nürnberg, Germany) was discontinued for at least 4 weeks. In all three patients the serum creatinine level was within the normal range. All of the patients had a histologically confirmed carcinoid tumour of the gastrointestinal tract and liver metastases and were candidates for ^{90}Y-DOTATOC therapy. Metastatic disease had been confirmed in all cases by recent morphological imaging with ultrasonography and computed tomography (CT). Based on CT images, tumour masses were calculated. The study was performed with the approval of the local ethical committee and all patients gave their informed consent prior to inclusion.

Radiopharmaceuticals. The somatostatin analogue DOTA-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC) was labelled at the Institute of Nuclear Chemistry, University of Mainz, Germany, with yttrium-86 (produced at the PETtrace cyclotron, Department of Radiopharmacy, University of Tübingen, Germany), as described previously [6, 7]. Prior to labelling, a final purification using ion-exchange chromatography was performed. The labelling yields were >98.5% as measured by instant thin-layer-chromatography (ITLC; 0.1 *M* Na citrate, Si60 plates, Merck, Darmstadt, Germany; 0.1 *M* NaOAc/MeOH (30/70), HPTLC-C18 plates, Merck, Darmstadt, Germany). Administered specific activity was 11–24 GBq/µ*M*. Patients received a mean injected dose of 137 MBq (range 77–186 MBq).

^{111}In-DTPA-D-Phe^{1}-octreotide was prepared from a commercially available kit (OctreoScan) provided by Mallinckrodt (Petten, The Netherlands) according to the manufacturer's instructions. The labelling yields always exceeded 95% as analysed by ITLC with 0.1 mol/l Na citrate buffer pH 5 as the solvent. The mean injected dose per patient was 161 MBq (range 110–187 MBq)

Pharmacokinetic studies. In order to determine the radiopeptide biological clearance, blood samples were drawn at 1, 2, 3, 4, 5, 10, 15, 20, 30 and 45 min and 1, 3, 6, 10, 20, 30, 48 and 72 h after injection. All urine produced up to 72 h p.i was collected as separate samples at the various time intervals possible. The activity in blood and urine samples was determined using a gamma counter, with a 20% reading window centred on the 173- and 247-keV peaks for ^{111}In and the 511-keV peak for ^{86}Y. The efficiency of the system was determined by counting a calibrated source of the respective nuclide with the same geometry used for the samples. Radioactivity measurements were corrected for physical decay and expressed as percent of injected dose (% ID) versus time [% ID_{biol} (*t*)]. The time-activity curve in the blood was generally fitted with a three-exponential function. The activity in urine samples was used to obtain the cumulative % ID versus time [% ID_{biol} (*t*)]. In order to minimise individual variation in the pharmacokinetics, the patients were instructed to drink at least 2.5 l a day, starting 1 day before the tracer injection.

Scintigraphic imaging. PET imaging with ^{86}Y-DOTATOC was performed with an ECAT EXACT 922 scanner (Siemens/CTI, Knoxville, Tenn.). Following a transmission scan with an external ^{68}Ga/^{68}Ge ring source, a 45-min dynamic acquisition protocol was performed starting at the time of injection. The field of view (16 cm) was centred on the liver. Additional PET scans of the thorax and abdomen were performed 1, 2, 4, 6, 10, 20, 30 and 48 h post injection (p.i.) in three or four bed positions with emission scans and transmission scans for attenuation correction. All emission scans were done in the 2D mode. The energy window ranged from 350 to 650 keV. Data were reconstructed by filtered backprojection using a Hanning filter (cut-off frequency 0.5 bin^{-1}). The imaging and reconstruction algorithms were previously optimised for the used camera system based on phantom studies with ^{86}Y using methodological approaches described elsewhere [6].

After injection of ^{111}In-DTPA-octreotide, whole-body acquisition was performed immediately and at 1, 2, 3, 6, 10, 20, 30, 48 and 72 h p.i., using a triple-head gamma camera (IRIX, Marconi, Cleveland, Ohio) with a medium-energy general-purpose parallel-hole collimator (MEGP-Par). The whole-body images were obtained in the anterior and posterior views, with a 256×1024 pixel matrix and a scan speed of 6 cm/min. To verify that the activity localisation corresponded to the tumour lesions documented by CT scans, single-photon emission tomography (SPET) studies were obtained 4–5 and 24 h after injection (120 views/3°, 50 s/view, 128×128 matrix). Raw data were reconstructed by filtered backprojection employing a ramp filter, post-filtered using a low-pass Butterworth filter (order 5.0, cut-off 0.40) and corrected for attenuation (coefficient 0.09).

Biodistribution and dosimetry. For biodistribution of ^{86}Y-DOTATOC, regions of interest (ROIs) were drawn on the transverse images for organs and tumour lesions. Mean activity per volume was calculated, decay corrected and related to the injected dose. Following decay correction for ^{90}Y, data were expressed as % ID (*t*) [6, 7].

To evaluate the biodistribution of ^{111}In-DTPA-octreotide, ROIs were drawn manually on planar images over the total body, tumour lesions and normal organs, i.e. heart, lungs, liver, spleen and kidneys, on the anterior and posterior views, and the geometric mean was calculated. Parts of organs showing tumour infiltration or superimposition were excluded from the evaluation of organ uptake. All data were corrected for decay and the whole-body activity acquired immediately after injection was defined as 100% of the injected dose [8]. Data for whole body, organs and tumour lesions were expressed as % ID_{biol} (*t*).

The resulting time-activity data from gamma and PET scans were fitted by three exponential curves. The residence times were determined by using these data and the respective half-lives of ^{111}In, ^{86}Y and ^{90}Y. The residence time for the red marrow was calculated from the residence time in the plasma, with the assumption of a uniform activity distribution, an equivalent clearance and non-specific uptake of the tracer in the bone marrow, whereas the specific activity in red marrow was considered to be 25% of the specific activity in the plasma [9]. To calculate the absorbed dose to the bladder wall, the residence time for bladder contents was calculated following the dynamic urine bladder model, based on the experimental curve of the cumulative activity eliminated in the urine [10]. The voiding interval assumed here was 2 h. Based on these data, doses to organs, tumour lesions and the whole body for ^{90}Y-DOTATOC therapy were estimated on the basis of the MIRD concept. Absorbed doses were calculated by applying the MIRDOSE3.1 and IMEDOSE software [11, 12]. Additionally, doses for the performed ^{111}In-DTPA-octreotide and ^{86}Y-DOTATOC investigations were estimated.

Results

Pharmacokinetic studies

Patients showed no clinical adverse reaction and no side-effects after the intravenous injection of ^{86}Y-DOTATOC or ^{111}In-DTPA-octreotide. Figure 1a displays the blood clearance of both tracers for all three patients. In all cases, the activity in blood decreased to less than 10% within the first 3 h and to less than 1% within 13–15 h. As shown in Fig. 1b, the mean (range) cumulative activity excreted in the urine and expressed as % injected dose was 47.6% ID (40.3–54.8) versus 52.2% ID (44.6–59.9) 5 h p.i. and 60.1% ID (53.2–67.0) versus 68.8% ID (62.6–75.0) 24 h p.i. for ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide, respectively. When comparing the two tracers, there were no significant differences in the kinetics of ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide regarding blood clearance and urinary excretion.

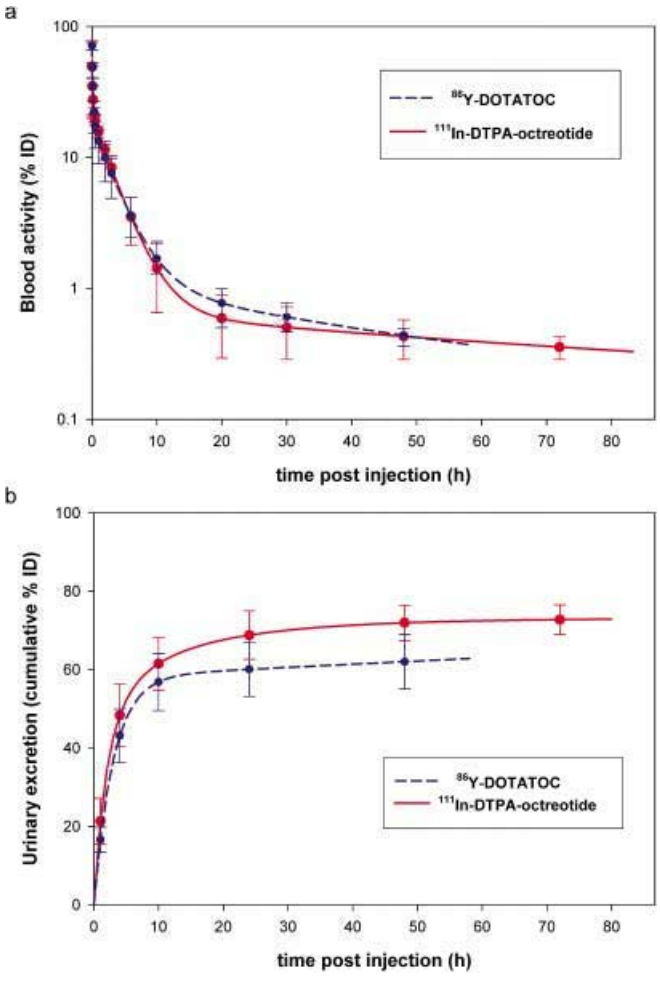

Fig. 1a, b. Biological clearance of ^{86}Y-DOTATOC (*dashed curves, blue*) and ^{111}In-DTPA-octreotide (*solid curves, red*) from the blood (**a**) and excretion in the urine (**b**). Mean values and ranges (*error bars*) for the investigated patients are reported in a semi-logarithmic scale. The curves of **a** show a rapid decrease in the blood activity without relevant differences between the tracers. In **b**, profiles of the cumulative activity excreted in the urine, expressed as $\%ID_{biol}(t)$, are displayed for both tracers. Again, the data are expressed as mean values and ranges (*error bars*) for the investigated patients

Biodistribution and dosimetry

The distribution patterns of ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide were similar in the initial phase, with rapid visualisation of the kidneys. Four hours after injection, tracer accumulation in the liver, spleen, kidneys and tumour lesions exceeded background radioactivity. Figure 2 shows anterior and posterior PET and SPET projection images 4 h and 24 h p.i. in one patient (#2) with extensive metastatic disease affecting the liver and para-aortic lymph nodes. For comparison, images are presented based on the maximum intensity projection. Although in both investigations the tumour lesions are visible with high contrast, the uptake of ^{86}Y-DOTATOC is more intense than that of ^{111}In-DTPA-octreotide. This is especially evident when the uptake in the kidneys and the spleen is compared with that in the para-aortic lymph nodes. Due to the higher spatial resolution of PET, the appearance of the metastases is clearer and more detailed. In contrast to ^{86}Y-DOTATOC images, ^{111}In-DTPA-octreotide images showed clearly visible tracer uptake in the intestine in all three patients approximately 24 h p.i. (Fig. 2c.).

The higher uptake of ^{86}Y-DOTATOC in metastatic lesions that is apparent in the images can be verified by the evaluation of biodistribution. Figure 3 summarises the time-activity curves of patient #2, expressed as % ID per organ or tumour lesion versus time. When comparing the two tracers, it is apparent that the kinetics in the organs are relatively similar, the similarity being most pronounced for the liver and least pronounced for the

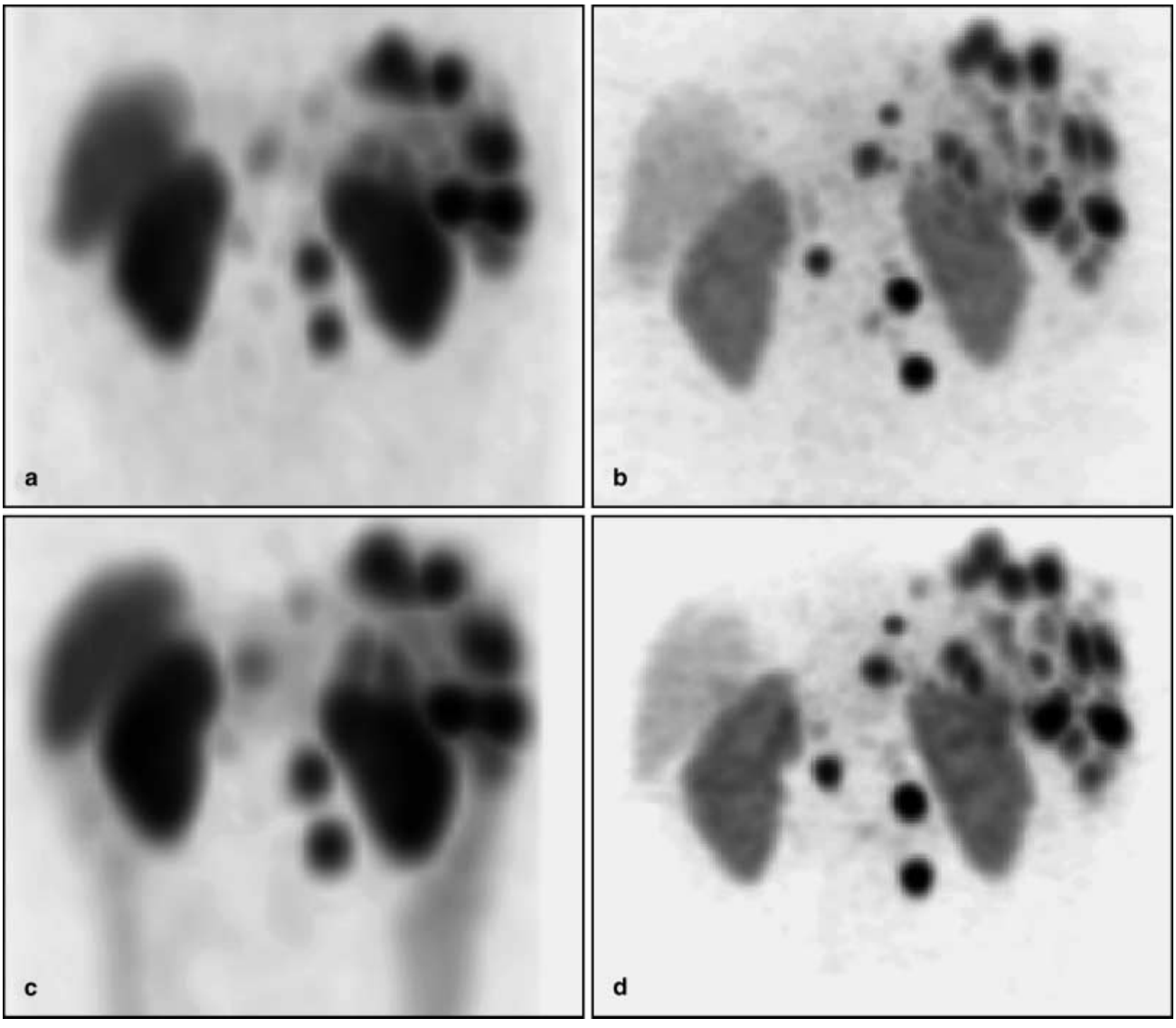

Fig. 2a–d. Scintigraphic abdominal images acquired 4 h (**a, b**) and 24 h (**c, d**) after injection of ^{111}In-DTPA-octreotide (**a, c**) and ^{86}Y-DOTATOC (**b, d**) in the same patient (#2), who had extensive hepatic and para-aortic metastases of a carcinoid tumour. Posterior views of SPET and PET images processed on the basis of the maximum intensity projection are shown

Table 1. Mean (±SD) residence times (τ) and absorbed doses (D) of organs and the total body and the effective dose (ED) for ^{90}Y-DOTATOC therapy based on ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide investigations in all patients

Source/target organ	Based on ^{111}In-DTPA-octreotide:		Based on ^{86}Y-DOTATOC:	
	τ_{organ}(h)	D_{organ} (mGy/MBq)	τ_{organ}(h)	D_{organ} (mGy/MBq)
Intestine wall	0.471±0.096	0.620±0.427	–	0.049±0.002
Kidneys	1.673±0.447	3.013±0.805	1.514±0.782	2.728±1.408
Liver	2.108±0.525	0.594±0.148	2.327±0.525	0.656±0.148
Other tissue	–	0.042±0.008	–	0.049±0.002
Red marrow	0.044±0.008	0.042±0.008	0.038±0.010	0.049±0.002
Spleen	0.946±0.521	2.786±1.535	0.788±0.669	2.320±1.970
Urinary bladder wall	0.870±0.004	0.764±0.504	0.780±0.170	1.030±0.225
Remainder of the body	5.389±1.051	–	6.361±0.206	–
Total body	–	0.085±0.011	–	0.082±0.014
ED (mSv/MBq)		0.346±0.166		0.215±0.066

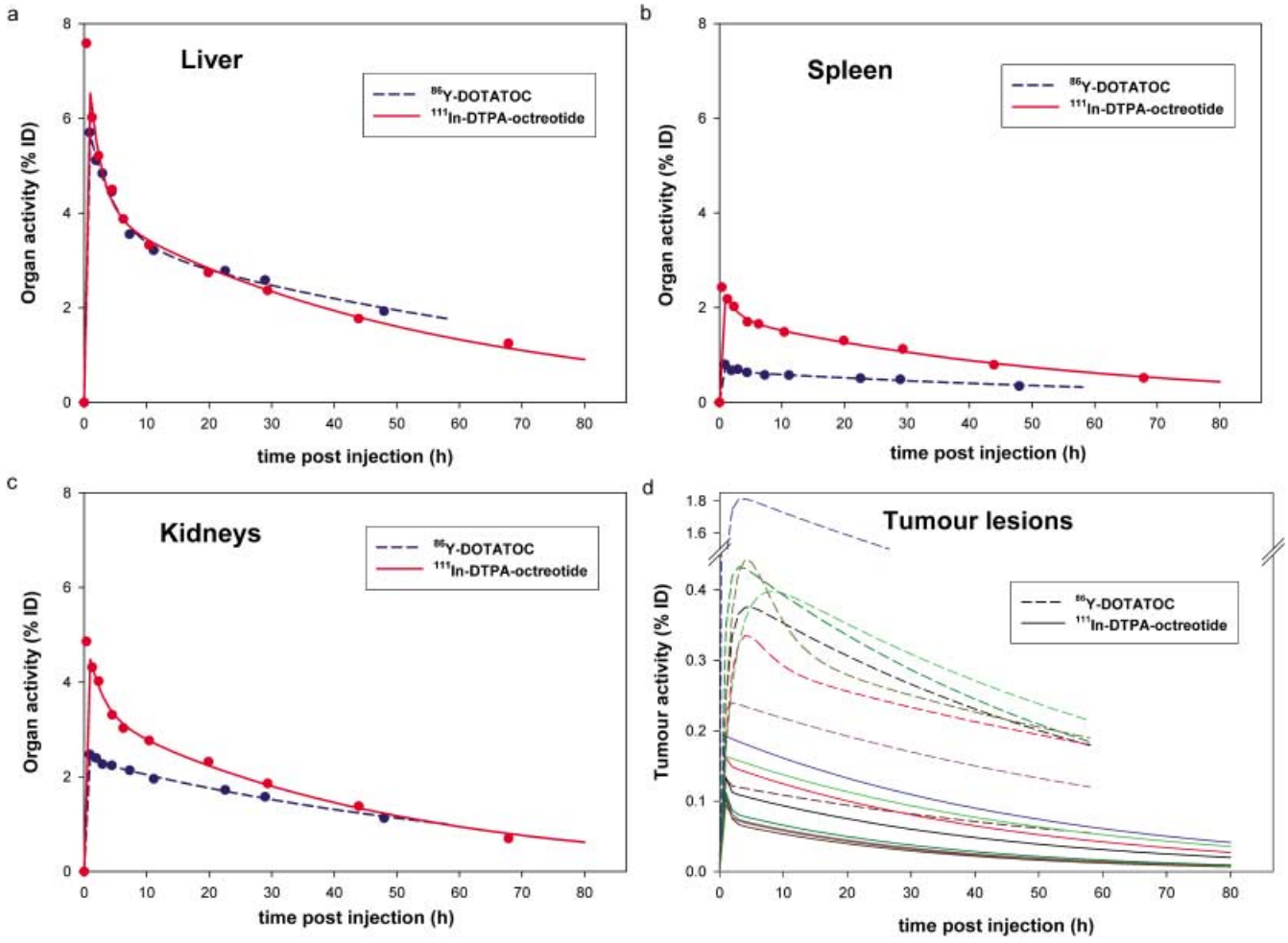

Fig. 3a–d. Time-activity curves for ^{90}Y-DOTATOC based on ^{86}Y-DOTATOC (*dashed curves*) and ^{111}In-DTPA-octreotide (*solid curves*) in patient #2 (see also Fig. 2). Measured values and the corresponding three-exponential fitted curves are expressed as a percentage of the administered dose (% ID) for liver (**a**), spleen (**b**) and kidneys (**c**). Time-activity curves of eight metastases based on both tracers are also shown (**d**). Since for every metastatic lesion a separate colour is selected, the kinetics are directly comparable. Note that for all metastases much higher uptake is calculated based on ^{86}Y-DOTATOC as compared with ^{111}In-DTPA-octreotide

spleen. By contrast, the uptake kinetics of the metastases show marked differences, with much higher uptake and slower washout for ^{86}Y-DOTATOC.

As shown in Table 1, the mean residence times (τ_{organ}) based on the time-activity curves of either ^{86}Y-DOTATOC or ^{111}In-DTPA-octreotide and the mean radiation absorbed doses (D_{organ}) in normal tissue calculated for ^{90}Y-DOTATOC therapy reflected these differences consistently in all of the patients. The estimated total body dose was similar for the calculations based on ^{111}In-DTPA-octreotide and ^{86}Y-DOTATOC: $D_{total\ body}$ 0.085±0.011 vs 0.082±0.014 mGy/MBq, respectively (mean±SD). The same was true for the estimated absorbed dose to the red marrow (0.042±0.008 vs 0.049±0.002 mGy/MBq). The effective dose (ED) showed some differences (ED 0.346±0.166 vs 0.215±0.066 mSv/MBq) that were mainly due to the intestinal uptake of ^{111}In-DTPA-octreotide. As expected, the mean dose calculated for the intestinal tract based on ^{111}In-DTPA-octreotide was higher than that based on ^{86}Y-DOTATOC (0.620±0.427 vs 0.049±0.002 mGy/MBq). However, the absorbed doses for the other most important organs were comparable, with mean differences between the two calculations of 9.4% for liver, 10.5% for kidneys, 20.1% for spleen and 25.8% for the urinary bladder.

Although the data were relatively consistent for intertracer estimates in these organs within an individual patient, this was not true when comparing the absorbed doses between subjects. Whereas calculated residence times and absorbed doses based on ^{86}Y-DOTATOC were similar in liver (τ_{liver} 1.592–2.789 h; D_{liver} 0.449–0.786 mGy/MBq), organ doses in kidneys ($\tau_{kidneys}$ 0.546–2.461 h; $D_{kidneys}$ 0.983–4.430 mGy/MBq) and spleen (τ_{spleen} 0.065–1.677 h; D_{spleen} 0.191–4.940 mGy/MBq) showed large differences between the patients. In Fig. 4, the organ doses (D_{organ}) for ^{90}Y-DOTATOC based on ^{86}Y-DOTATOC

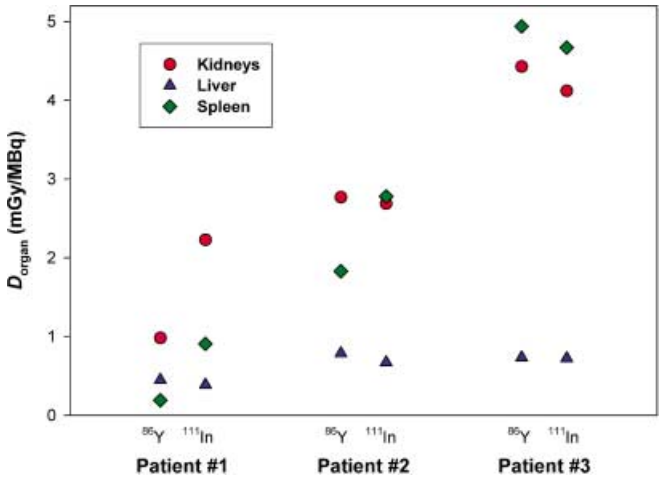

Fig. 4. Estimated absorbed doses to critical organs (D_{organ}) for ^{90}Y-DOTATOC therapy. The plots show the individual absorbed doses based on investigation with ^{86}Y-DOTATOC PET (*86Y*) and ^{111}In-DTPA-octreotide scintigraphy (*111In*)

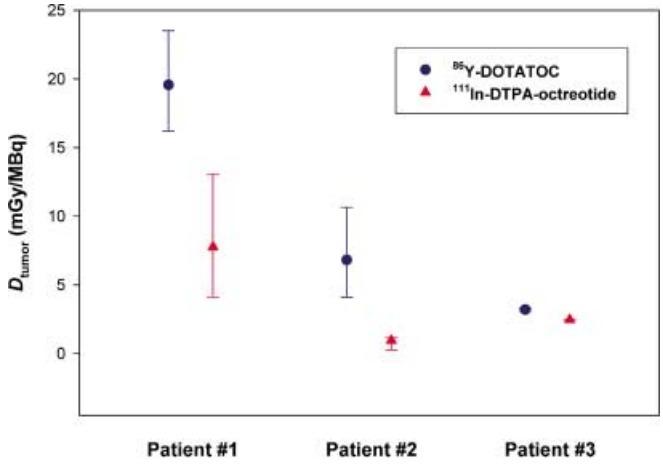

Fig. 5. Estimated absorbed doses to tumour lesions (D_{tumour}) for ^{90}Y-DOTATOC therapy. For each patient the mean and range of D_{tumour} based on investigation with ^{86}Y-DOTATOC PET and ^{111}In-DTPA-octreotide scintigraphy are shown

and on ^{111}In-DTPA-octreotide are compared for each patient.

In contrast to organ doses, the calculated absorbed doses in tumour lesions were consistently higher when based on ^{86}Y-DOTATOC than when based on ^{111}In-DTPA-octreotide. The mean differences were 61%, ranging between 23.1% and 85.9% (Fig. 5). The calculated mean dose to tumour lesions in each patient for therapy with ^{90}Y-DOTATOC was 19.58, 6.82 and 3.21 mGy/MBq (for patients #1, #2 and #3, respectively) based on ^{86}Y-DOTATOC and 7.76, 0.96 and 2.46 mGy/MBq based on ^{111}In-DTPA-octreotide.

Finally, the radiation doses caused by the ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide investigations themselves were estimated. For the ^{86}Y-DOTATOC studies, the individual effective doses (ED) were 0.031, 0.037 and 0.044 mSv/MBq (in patients #1, #2 and #3, respectively), while for the ^{111}In-DTPA-octreotide studies they were 0.044, 0.053 and 0.059 mSv/MBq.

Discussion

In this study, dosimetric analyses based on ^{86}Y-DOTATOC and ^{111}In-DTPA-octreotide revealed differences in organ and tumour distribution due to differences in the pharmacokinetics of these tracers. Furthermore, a marked variability in the individual biodistribution could be demonstrated in this small patient sample. Both aspects are of relevance for peptide receptor radionuclide therapy with ^{90}Y-DOTATOC.

As the positron-emitting ^{86}Y-DOTATOC is chemically identical to the therapeutically applied tracer, results obtained with this radiopharmaceutical and PET, which allows more accurate quantification, can be regarded as more reliable than those obtained with the easily accessible, commercially available analogue ^{111}In-DTPA-octreotide. In this respect, the quantitative data obtained with ^{86}Y-DOTATOC can be regarded as the gold standard.

Relevant differences between the tracers in terms of blood clearance and elimination via the urine were not observed in the three patients investigated in this study. Our data, therefore, do not confirm the suggestion that the urinary excretion of DOTATOC might be faster than that of other somatostatin analogues owing to the increased hydrophilicity of the DOTA modified peptide, in which the amino acid Phe^3 is replaced by Tyr^3 [8]. If the differences in hydrophilicity have an effect on tracer elimination, it may not be very pronounced and may not have been apparent in this small sample of patients in whom rigidly standardised hydration was not performed.

The estimated mean effective dose caused by ^{111}In-DTPA-octreotide itself was 0.052 mSv/MBq and well in accordance with the data reported in the literature [1]. The effective dose estimated for ^{86}Y-DOTATOC was in the same order of magnitude, so that this tracer has no relevant disadvantage as far as the radiation burden for the patient is concerned. To compare the data collected from both tracers and to obtain results with more practical relevance, the dosimetric calculations were related to a virtual therapy with ^{90}Y-DOTATOC. The obtained data do not reflect the true therapeutic situation of these patients, all of whom subsequently underwent therapy with standard doses, since the simultaneous infusion of amino acids performed in the therapeutic situation in order to lower the radiation burden was not considered [3, 7].

Although the dosimetric calculations were based on the MIRD concept for both tracers, fundamental differences in the generation of the organ curves exist, since the data from the PET studies were obtained from attenuation-corrected transaxial images, whereas the data

from the ^{111}In-DTPA-octreotide studies were obtained from planar images. Furthermore, the reconstructed 2D PET tomograms are expected to be less affected by scatter than the non-processed whole-body scintigrams, although this issue has not been examined in detail. However, since the residence times calculated for different organs (τ_{organ}) were quite similar, severe systematic effects probably did not confound the results. We chose conjugate planar imaging rather than SPET to derive the ^{111}In-DTPA-octreotide based dosimetry because SPET would have required a constant distribution of the radiopharmaceutical during imaging and would not have allowed the data to be related to a true baseline [11]. Furthermore, the chosen approach reflects the commonly used procedure for dosimetry based on gamma-emitting radioisotopes, whereas an approach based on SPET would be more unusual [11].

Both approaches used in this study revealed the highest tracer uptake in kidneys, followed by spleen, urinary bladder and liver, thereby identifying these organs as critical during therapy with ^{90}Y-DOTATOC [2, 13]. Dosimetry with ^{111}In-DTPA-octreotide overestimated the radiation burden in kidneys and spleen as compared with ^{86}Y-DOTATOC. However, there was a good correlation between the dosimetric data obtained with ^{111}In-DTPA-octreotide and ^{86}Y-DOTATOC for the individual patients in our study. This is in contrast to preliminary data previously reported by Barone et al. [14]. This group used a SPET-based method for ^{111}In-DTPA-octreotide dosimetry and reported only a weak correlation with ^{86}Y-DOTATOC dosimetry.

Even more relevant for therapy planning might be the fact that with ^{111}In-DTPA-octreotide there was a severe underestimation of the doses achieved in the metastatic lesions. This finding is in agreement with recent studies performed in humans that have demonstrated significantly higher uptake in somatostatin receptor-positive tissue following administration of ^{111}In-DOTATOC compared to ^{111}In-DTPA-octreotide [2, 13] and with the preliminary results comparing ^{111}In-DTPA-octreotide and ^{86}Y-DOTATOC [14]. This may be explained by the higher hydrophilicity of DOTATOC, resulting in a higher in vivo receptor affinity and a higher specific uptake in somatostatin receptor-expressing tissue [4, 15]. The relevance of these different findings in a clinical context might be illustrated by the fact that, according to the calculations with ^{111}In-DTPA-octreotide, patient #2 would receive a dose of 9.95 Gy in the kidneys and 4.29 Gy in the metastasis with the highest uptake based on a therapeutic dose of 3,700 MBq ^{90}Y-DOTATOC, compared with 10.25 Gy and 39.4 Gy when the dosimetric estimate is based on ^{86}Y-DOTATOC.

When comparing ^{111}In-DOTATOC with ^{86}Y-DOTATOC, it may be concluded that the latter is advantageous because animal data have shown that uptake of Y-labelled DOTATOC in somatostatin receptor-positive tissues and internalisation into cells are significantly higher than with the In-labelled compound, suggesting that the DOTA chelator is more appropriate for complexation of Y than of In [4, 13, 16]. In addition, given the inherent advantages of PET, investigations with the positron emitter ^{86}Y-DOTATOC should lead to a higher sensitivity in the detection of small tumour lesions, increasing diagnostic accuracy [17].

Another relevant finding of this study was the remarkable inter-individual differences observed with both dosimetric approaches when the absorbed doses in normal tissues were calculated for ^{90}Y-DOTATOC therapy. This variability may be related to several factors that are not necessarily clinically apparent, such as differences in renal function, metabolism or receptor density of parenchymatous organs [1]. This underlines the paramount importance of individual dosimetry for ^{90}Y-DOTATOC therapy if severe side-effects such as nephrotoxicity are to be avoided [3]. For this purpose, dosimetry based on ^{111}In-DTPA-octreotide already seems to give reasonable results, although it does not allow for a more accurate PET-based estimation of the tumour dose achieved.

Conclusion

Individual dosimetry before peptide receptor radionuclide therapy with ^{90}Y-DOTATOC appears necessary considering the large differences in organ doses between individual patients. Compared to dosimetry with ^{86}Y-DOTATOC, dosimetry with ^{111}In-DTPA-octreotide yields similar dose estimates for the effective dose and for individual organ doses, but underestimates tumour uptake. Therefore, if possible, dosimetry should be performed with the PET tracer ^{86}Y-DOTATOC, which is chemically identical to the therapeutic agent.

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