

# A comparison of $^{111}\text{In}$ -DOTATOC and $^{111}\text{In}$ -DOTATATE: biodistribution and dosimetry in the same patients with metastatic neuroendocrine tumours

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**Abstract.** [Yttrium-90-DOTA-Tyr<sup>3</sup>]-octreotide (DOTA-TOC) and [<sup>177</sup>Lu-DOTA-Tyr<sup>3</sup>-Thr<sup>8</sup>]-octreotide (DOTA-TATE) are used for peptide receptor-mediated radionuclide therapy (PRMRT) in neuroendocrine tumours. No human data comparing these two compounds are available so far. We used  $^{111}\text{In}$  as a surrogate for  $^{90}\text{Y}$  and  $^{177}\text{Lu}$  and examined whether one of the  $^{111}\text{In}$ -labelled peptides had a more favourable biodistribution in patients with neuroendocrine tumours. Special emphasis was given to kidney uptake and tumour-to-kidney ratio since kidney toxicity is usually the dose-limiting factor. Five patients with metastatic neuroendocrine tumours were injected with 222 MBq  $^{111}\text{In}$ -DOTATOC and  $^{111}\text{In}$ -DOTATATE within 2 weeks. Up to 48 h after injection, whole-body scans were performed and blood and urine samples were collected. The mean absorbed dose was calculated for tumours, kidney, liver, spleen and bone marrow. In all cases  $^{111}\text{In}$ -DOTATATE showed a higher uptake (%IA) in kidney and liver. The amount of  $^{111}\text{In}$ -DOTATOC excreted into the urine was significantly higher than for  $^{111}\text{In}$ -DOTATATE. The mean absorbed dose to the red marrow was nearly identical.  $^{111}\text{In}$ -DOTATOC showed a higher tumour-to-kidney absorbed dose ratio in seven of nine evaluated tumours. The variability of the tumour-to-kidney ratio was high and the significance level in favour of  $^{111}\text{In}$ -DOTATOC was  $P=0.065$ . In five patients the pharmacokinetics of  $^{111}\text{In}$ -DOTATOC and  $^{111}\text{In}$ -DOTATATE was found to be comparable. The two peptides appear to be nearly equivalent for PRMRT in neuroendocrine tumours, with minor advantages for  $^{111}\text{In}/^{90}\text{Y}$ -DOTATOC; on this basis, we shall

continue to use  $^{90}\text{Y}$ -DOTATOC for PRMRT in patients with metastatic neuroendocrine tumours.

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## Introduction

Somatostatin receptors have been identified in high density on neuroendocrine tumours as well as on tumours of the central nervous system, the breast, the lung and the lymphatic tissue [1]. To demonstrate the presence of somatostatin receptors in vivo, scintigraphy with radiolabelled somatostatin analogues such as [ $^{111}\text{In}$ -DTPA-D-Phe<sup>1</sup>]-octreotide (Octreoscan) has become the gold standard [2]. Peptide receptor-mediated radionuclide therapy (PRMRT) has been used for several years in the treatment of progressive, metastasised, somatostatin receptor-positive tumours. Both somatostatin analogues, [ $^{90}\text{Y}$ -DOTA-Tyr<sup>3</sup>]-octreotide (DOTATOC) and [ $^{177}\text{Lu}$ -DOTA-Tyr<sup>3</sup>-Thr<sup>8</sup>]-octreotide (DOTATATE), have been used for this purpose and have shown encouraging results [3–6]. Recently, Kwekkeboom et al. showed that  $^{177}\text{Lu}$ -DOTATATE had an up to fourfold higher tumour uptake than [ $^{111}\text{In}$ -DTPA]-octreotide in six patients [7]. Moreover, Reubi et al. have shown that  $\text{Y}^{(III)}$ -DOTATATE has an approximately sevenfold higher binding affinity to the somatostatin receptor subtype 2 (hsst2) compared with  $\text{Y}^{(III)}$ -DOTATOC [8], which suggests that  $^{111}\text{In}/^{90}\text{Y}$ -DOTATATE would show a higher tumour uptake in patients. However, no patient data comparing these two compounds are available so far.

Therefore, the aim of this study was to compare the pharmacokinetics of  $^{111}\text{In}$ -DOTATOC and  $^{111}\text{In}$ -DOTATATE in the same patients. Special emphasis was placed on the mean absorbed doses for tumour, kidney

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and bone marrow since the dose-limiting organs for PRMRT with radiolabelled somatostatin analogues are usually the kidneys and the bone marrow [3, 4, 9]. In addition,  $^{111}\text{In-DOTATOC}/^{111}\text{In-DOTATATE}$  was taken as a surrogate for  $^{90}\text{Y-DOTATOC}/^{90}\text{Y-DOTATATE}$  and the calculated mean absorbed doses of  $^{90}\text{Y-DOTATOC}$  were compared with the doses of this radiopeptide known from the literature [10–13].

## Materials and methods

**Patients.** Five male patients (age 49–73, mean 62 years) (Table 1) with known metastatic neuroendocrine tumours were injected with 222 MBq  $^{111}\text{In-DOTATOC}$  and 222 MBq  $^{111}\text{In-DOTATATE}$ , with an interval of 2 weeks between the administrations. In three patients,  $^{111}\text{In-DOTATATE}$  was injected first, while in two,  $^{111}\text{In-DOTATOC}$  was injected first. In two patients the primary tumour was in the pancreas. In three patients the origin of the disease was unknown. None of the patients had received medication with somatostatin analogues (Octreotide s/c or LAR, Novartis Pharma; Lanreotide, Ipsen Ltd.) within the 8 weeks before the examinations. All patients had a histologically confirmed neuroendocrine tumour and had been treated with  $^{90}\text{Y-DOTATOC}$  before. There were at least 14 months between the last therapy and the beginning of the study (14–25 months, mean 20.25 months). Metastatic disease had been confirmed in all cases by recent morphological imaging with magnetic resonance imaging (MRI), computed tomography (CT) or ultrasonography. Based on these examinations, the tumour volumes were calculated. The study was approved by the Swiss authorities and by the local ethical committee (Ethikkommission beider Basel). All patients gave informed consent.

**Radiopharmaceuticals.** Both somatostatin analogues, DOTATOC and DOTATATE, were synthesised in house according to a previously published procedure [8, 14] and radiolabelled with  $^{111}\text{In}$  as published previously [15].  $^{111}\text{In}$  was purchased from Tyco Healthcare (Petten, The Netherlands). The labelling yield and the radiopharmaceutical purity were checked using  $\text{C}_{18}$  reversed-phase high-performance liquid chromatography.

**Imaging.** All images were acquired with a dual-head gamma camera Picker Prism 2000 XP (Philips, Eindhoven, The Netherlands). The windows were centred over both  $^{111}\text{In}$  photon peaks (245 and 172 keV) with a width of 20%. Parallel-hole, medium-energy general-purpose collimators were used. For both compounds, the same protocol was followed: dynamic imaging up to 20 min post injection with a field of view over the kidneys and liver from the posterior projection (80 images, 15 s per image). Whole-body scans were obtained 1, 2, 4, 24 and 48 h after injection. The acquisition time for all whole-body scans was 15 min.

**Measurement of radioactivity in blood and urine.** Blood samples were drawn 10, 20, 30 and 60 min and 2, 4, 24 and 48 h after injection. Urine was collected in four intervals: 0–2, 2–4, 4–24 and 24–48 h after injection. Radioactivity in blood and urine was measured with a gamma counter (Cobra II Autogamma, Packard, A Canberra Company).

**Pharmacokinetics and dosimetry.** Regions of interest (ROIs) were drawn manually on the whole-body scans from the anterior and posterior projections for the whole body, the kidneys, the spleen,

**Table 1.** Patient details

Patient	Age (yrs)	Histology and primary tumour
1	69	Neuroendocrine tumour of the pancreas
2	65	Neuroendocrine tumour of unknown origin
3	73	Neuroendocrine tumour of unknown origin
4	53	Neuroendocrine tumour of unknown origin
5	49	Neuroendocrine tumour of the pancreas

the liver, the bladder and tumour lesions. The Odyssey XP program was used. Background regions were placed close to the ROIs for background correction. Parts of the organs showing tumour infiltration or superimposition were excluded from the evaluation of organ uptake. The geometric mean value, between anterior and posterior, was taken and corrected for attenuation and physical decay. Whole-body activity acquired 1 h after injection was defined as 100% of the injected activity (IA). The patients did not empty the bladder during this period. All data for the whole body, organs and tumour lesions were expressed in %IA. A compartment model as described previously was used to calculate the residence time from the time-activity data resulting from the scans [10]. The activity in blood was fitted by three exponential curves. The residence times were determined using these data and the respective half-lives of  $^{111}\text{In}$  and  $^{90}\text{Y}$ . Assuming no specific uptake in the red marrow, a uniform distribution of the activity, and that the red marrow clearance was the same as in blood, the dose to the red marrow was calculated with a correction factor of 1 from the residence time in blood as published previously [10].

**Statistics.** Paired *t* test was used to determine statistical significance. Differences at the 95% confidence level ( $P < 0.05$ ) were considered significant.

## Results

Patients showed no clinical adverse reactions and no side-effects after the intravenous injection of  $^{111}\text{In-DOTATOC}$  or  $^{111}\text{In-DOTATATE}$ .

### Pharmacokinetic studies

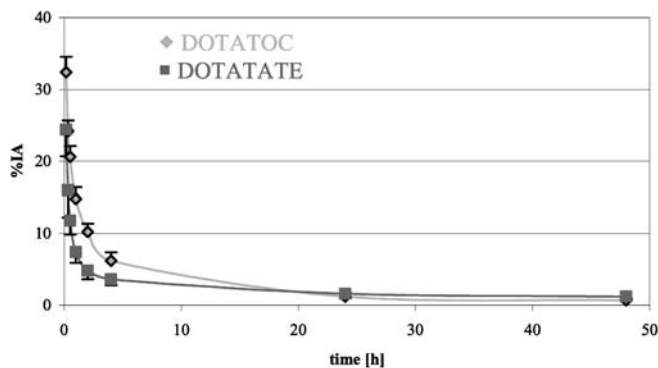
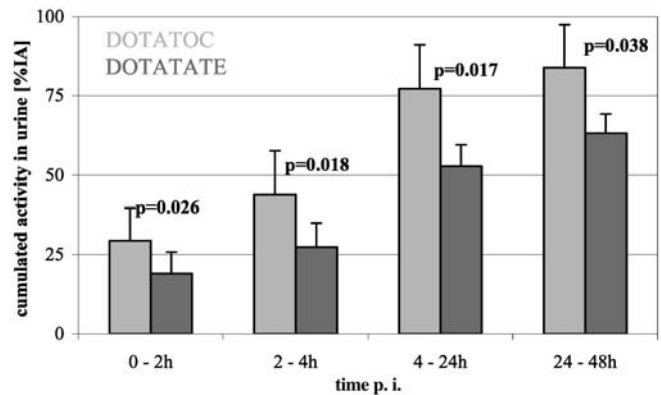
Figure 1 displays the mean plasma radioactivity (and standard deviation) expressed as %IA. The clearance of both peptides was fast. The time-activity in blood could be fitted by three exponential curves. In all patients and for both radiopeptides, the activity in blood decreased to less than 10% within the first 4 h.  $^{111}\text{In-DOTATOC}$  showed a somewhat slower clearance initially. After 24 and 48 h, a slightly higher amount of  $^{111}\text{In-DOTATATE}$  was found in the blood of all patients. The mean residence time ( $\tau$ ) was 1.178 h ( $\text{SD} \pm 0.19$  h) for  $^{111}\text{In-DOTATOC}$  and 1.156 h ( $\text{SD} \pm 0.32$  h) for  $^{111}\text{In-DOTATATE}$ . Therefore, the mean absorbed dose to the red marrow was not significantly different between the two compounds (Table 2). Only a small interpatient variability was found (Table 3).

**Table 2.** Mean absorbed doses (mGy/MBq) for  $^{90}\text{Y}$ -DOTATOC (TOC) and  $^{90}\text{Y}$ -DOTATATE (TATE) derived from biodistribution data in five patients using the  $^{111}\text{In}$ -labelled peptides

Patient	Kidneys		Liver		Spleen		Red Marrow	
	TOC	TATE	TOC	TATE	TOC	TATE	TOC	TATE
1	2.95	3.53	0.88	1.31	15.5	13.4	0.15	0.15
2	3.15	3.62	0.82	2.39	1.71	3.3	0.17	0.16
3	3.60	3.62	1.33	2.16	4.8	7.74	0.17	0.20
4	2.59	3.58	1.15	1.34	4.71	7.98	0.19	0.16
5	1.91	5.17	0.41	1.18	6.12	18.5	0.15	0.13
Mean $\pm$ SD	2.84 $\pm$ 0.64	3.90 $\pm$ 0.71	0.92 $\pm$ 0.35	1.68 $\pm$ 0.56	6.57 $\pm$ 5.25	10.18 $\pm$ 5.87	0.17 $\pm$ 0.02	0.16 $\pm$ 0.03
<i>P</i> value	0.135		0.031		0.205		0.591	

**Table 3.** Comparison of mean absorbed doses ( $\pm$ SD) (mGy/MBq) for  $^{90}\text{Y}$ -DOTATOC derived from  $^{111}\text{In}$ -DOTATOC and  $^{86}\text{Y}$ -DOTATOC

	Forrer et al. this study	Cremonesi et al. [10]	Förster et al. [11]	Krenning et al. [12]
Derived from	$^{111}\text{In}$ -DOTATOC	$^{111}\text{In}$ -DOTATOC	$^{86}\text{Y}$ -DOTATOC	$^{86}\text{Y}$ -DOTATOC
Kidney	2.84 ( $\pm$ 0.64)	3.31 ( $\pm$ 2.22)	2.73 ( $\pm$ 1.41)	2.1 ( $\pm$ 0.78)
Liver	0.92 ( $\pm$ 0.35)	0.72 ( $\pm$ 0.57)	0.66 ( $\pm$ 0.15)	–
Spleen	6.57 ( $\pm$ 5.25)	7.62 ( $\pm$ 6.30)	2.32 ( $\pm$ 1.97)	1.83 ( $\pm$ 1.45)
Red marrow	0.17 ( $\pm$ 0.02)	0.03 ( $\pm$ 0.01)	0.049 ( $\pm$ 0.002)	0.11 ( $\pm$ 0.06)

**Fig. 1.** Blood clearance expressed as percentage of the injected activity (%IA) in the blood (mean  $\pm$  SD)**Fig. 2.** Cumulative activity excreted into the urine expressed as %IA (mean  $\pm$  SD)

Cumulative activity excreted into the urine was higher for  $^{111}\text{In}$ -DOTATOC in all samples and all patients (Fig. 2). For all periods (0–2, 2–4, 4–24 and 24–48 h) the difference was significant ( $P < 0.05$ ).

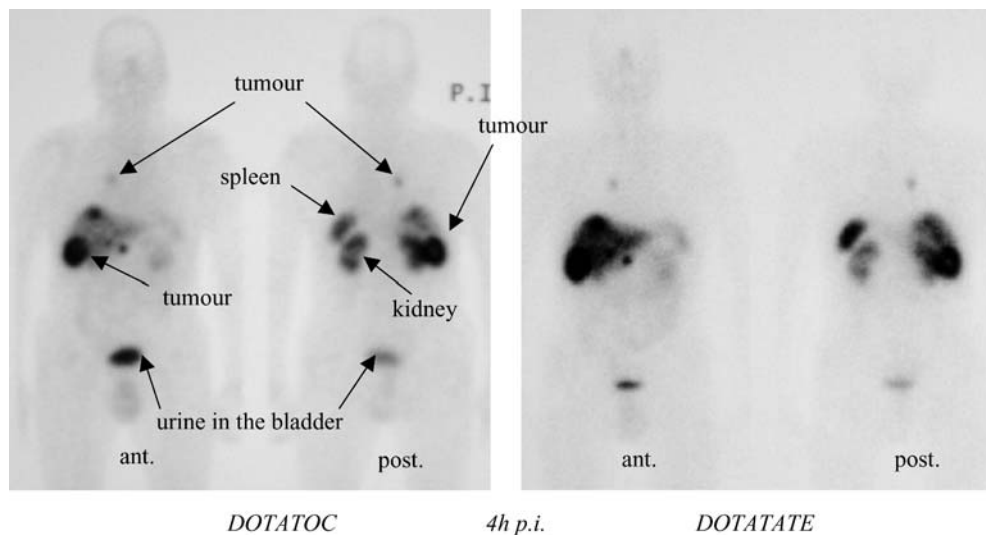
#### Biodistribution and dosimetry

The distribution pattern of  $^{111}\text{In}$ -DOTATATE was initially comparable to the pattern using  $^{111}\text{In}$ -DOTATOC. In four of the five patients a distinct specific uptake in tumour sites was seen after approximately 2 min. Also, there was fast visualisation of the liver, kidneys and spleen. The fifth patient showed no tumour uptake with either compound due to an impressive decrease in tumour load after  $^{90}\text{Y}$ -

DOTATOC therapy. In this patient, only two small liver metastases  $< 1$  cm were found on a recent CT scan.

We found higher mean absorbed doses to the kidneys and liver for  $^{111}\text{In}$ -DOTATATE. The calculated difference for  $^{90}\text{Y}$ , when taking  $^{111}\text{In}$  as a surrogate, was significant in the liver ( $P < 0.05$ ) but not in the kidneys ( $P = 0.135$ ). The dose to the spleen showed a high interpatient variability. Although in three patients the mean absorbed dose to the spleen for  $^{111}\text{In}$ -DOTATATE was higher (Table 2), the difference did not reach significance ( $P = 0.205$ ). The calculated absorbed doses for  $^{90}\text{Y}$ -DOTATOC (taking  $^{111}\text{In}$ -DOTATOC as the surrogate) for the various organs are comparable with the doses known from the literature [10–12]. Our values, along with literature data, are shown in Table 3.

**Fig. 3.** Whole-body scans of patient no. 2, 4 h after injection of 222 MBq  $^{111}\text{In}$ -DOTATOC (left) and  $^{111}\text{In}$ -DOTATATE (right). Better visualisation of the tumours in the liver can be seen in  $^{111}\text{In}$ -DOTATOC



**Table 4.** Mean absorbed tumour doses (mGy/MBq) for  $^{90}\text{Y}$ -DOTATOC and  $^{90}\text{Y}$ -DOTATATE derived from biodistribution data in nine tumours using the  $^{111}\text{In}$ -labelled peptides and the respective tumour-to-kidney ratio

Patient	Lesion (localisation)	Tumour doses (mGy/MBq)		Tumour-to-kidney ratio	
		DOTATOC	DOTATATE	DOTATOC	DOTATATE
1	1 (ln)	12.23	12.12	4.15	3.43
	2 (li)	33.34	24.26	11.30	6.87
2	3 (li)	2.88	4.60	0.91	1.27
	4 (li)	6.31	8.19	2.00	2.26
4	5 (b)	2.80	1.73	1.08	0.48
	6 (li)	41.66	55.54	16.08	15.51
	7 (li)	26.72	15.93	10.32	4.45
	8 (li)	15.77	12.13	6.09	3.39
5	9 (b)	2.37	6.15	1.24	1.18
Mean $\pm$ SD		16.01 $\pm$ 14.64	15.63 $\pm$ 16.40	5.91 $\pm$ 5.48	4.32 $\pm$ 4.36
<i>P</i> value		0.879		0.065	

(ln), Abdominal lymph node; (li), liver; (b), bone

Overall, nine metastases could be evaluated in scintigraphic images and correlated with a lesion on CT, MRI or sonography. In five of the nine lesions, a somewhat higher mean absorbed dose (mGy/MBq) was found for  $^{111}\text{In}$ -DOTATOC; however, high variability between the lesions was observed (Table 4).

Since most often the dose-limiting organ in therapy with radiopeptides is the kidneys, the absorbed dose ratio of lesion to kidneys will determine the therapeutic window. Due to the high variability in mean absorbed doses in the tumours, we found a high variability in the dose ratios as well. However, in seven out of nine lesions,  $^{111}\text{In}$ -DOTATOC showed a higher ratio and the difference in mean values almost reached significance ( $P=0.065$ ) (Table 4).

In two patients, whole-body scans 4, 24 and 48 h after injection showed better visualisation of liver metastases with  $^{111}\text{In}$ -DOTATOC. In the other three patients, the scans were visually identical. The better demarcation was due to the lower uptake in the normal liver. Findings in one of the patients with better demarcation of the liver metastases with  $^{111}\text{In}$ -DOTATOC are shown in Fig. 3.

## Discussion

In this study, both radiopeptides,  $^{111}\text{In}$ -DOTATOC and  $^{111}\text{In}$ -DOTATATE, showed the expected high specific uptake in somatostatin receptor-positive tissue. Visually, the results obtained with the two compounds were com-

parable, although better visualisation of some liver metastases was found with  $^{111}\text{In}$ -DOTATOC. The dosimetric analyses showed small differences between the radiopeptides, but a significantly higher mean absorbed dose to the liver was found for  $^{111}\text{In}$ -DOTATATE, and a favourable tumour-to-kidney ratio ( $P=0.065$ ) was calculated for  $^{111}\text{In}$ -DOTATOC. These findings were unexpected since data from animal models have shown a more favourable biodistribution for DOTATATE-derived radiopeptides [16]. Because the total administered therapeutic dose with radiolabelled somatostatin analogues is determined by tumour-to-kidney mean absorbed dose ratios (and/or tumour-to-red marrow absorbed dose ratios), these ratios are the most important parameters for therapeutic success. Slightly better results were found for  $^{111}\text{In}$ -DOTATOC in three of the four patients with well-defined uptake in metastases.

In this study, we used  $^{111}\text{In}$  as a surrogate for  $^{90}\text{Y}$ , as we assume high similarity between the tracers although differences in pharmacological parameters have been shown if DOTATOC is labelled with  $^{67}\text{Ga}/^{68}\text{Ga}$  instead of  $^{111}\text{In}$  [15]. In addition, de Jong et al. [17] showed differences in the biodistribution of  $^{111}\text{In}$ -DOTATOC and  $^{90}\text{Y}$ -DOTATOC in rats bearing the CA 20948 tumour. On the other hand, Froidevaux et al. [18] showed an essentially similar performance of  $^{111}\text{In}$ -DOTATOC and  $^{90}\text{Y}$ -DOTATOC when using the AR4-2J bearing mouse model.

The mean absorbed doses calculated for  $^{90}\text{Y}$ -DOTATOC are comparable with the absorbed doses published in the literature so far [9–13] (Table 3), confirming the accuracy of our methodology. Although the absorbed doses calculated for the red marrow were higher than the doses reported by Cremonesi et al. [10] and Förster et al. [11], they are comparable with the doses published by Krenning et al. [12] (Table 3).

A high interpatient absorbed tumour dose variability was found, which is not unexpected as receptor densities vary markedly among patients and tumours. This fact is well known from the literature [10–13].

A better tumour-to-kidney absorbed dose ratio can be achieved by co-infusion of amino acids, especially lysine and arginine [13, 19–21]. It is unclear whether the results obtained in comparing  $^{111}\text{In}$ -DOTATOC and  $^{111}\text{In}$ -DOTATATE would be the same if the measurements were to be performed with co-infusion of amino acids. The difference in charge (positive overall charge of  $^{111}\text{In}$ -DOTATOC and neutral charge of  $^{111}\text{In}$ -DOTATATE) might lead to different results with regard to the kidney absorbed dose after amino acid co-infusion.

The accuracy of the absolute values obtained by organ dosimetry using gamma-scintigraphy may still be limited owing to many potential sources of error. However, since the main aim of this study was to compare two compounds in the same patients with the same methods, this would not have affected the reliability of the findings.

We could not confirm the assumption, based on animal experiments, that  $^{90}\text{Y}$ -DOTATATE may have more favourable characteristics for PRMRT compared with  $^{90}\text{Y}$ -DOTATOC. Therefore, we will continue treatment with  $^{90}\text{Y}$ -DOTATOC.

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