Receptor-mediated radiotherapy with ^{90}Y-DOTA-D-Phe^{1}-Tyr^{3}-octreotide

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Abstract. A newly developed somatostatin radioligand, DOTA-[D-Phe^{1}-Tyr^{3}]-octreotide (DOTATOC), has been synthesised for therapeutic purposes, because of its stable and easy labelling with yttrium-90. The aim of this study was to determine the dosage, safety profile and therapeutic efficacy of ^{90}Y-DOTATOC in patients with cancers expressing somatostatin receptors. We recruited 30 patients with histologically confirmed cancer. The main inclusion criterion was the presence of somatostatin receptors as documented by ^{111}In-DOTATOC scintigraphy. ^{90}Y-DOTATOC was injected intravenously using a horizontal protocol: patients received equivalent-activity doses in each of three cycles over 6 months. The first six patients received 1.11 GBq per cycle and the four successive groups of six patients received doses increasing in 0.37-GBq steps. Toxicity was evaluated according to WHO criteria. No patient had acute or delayed adverse reactions up to 2.59 GBq ^{90}Y-DOTATOC per cycle (total 7.77 GBq). After a total dose of 3.33 GBq, one patient developed grade II renal toxicity 6 months later. The maximum tolerated dose per cycle has not yet been reached, although transient lymphocytopenia has been observed. Total injectable activity is limited by the fact that the maximum dose tolerated by the kidneys has been estimated at 20–25 Gy. Complete or partial tumour mass reduction occurred in 23% of patients; 64% had stable and 13% progressive disease. It is concluded that high activities of ^{90}Y-DOTATOC can be administered with a low risk of myelotoxicity, although the cumulative radiation dose to the kidneys is a limiting factor and requires careful evaluation. Objective therapeutic responses have been observed.

Keywords: Receptor-mediated radiotherapy – Somatostatin analogue – ^{90}Y/^{111}In-DOTATOC – Peptides

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Introduction

Since the discovery, in the late 1960s, of the inhibitory properties of native tetradecapeptide somatostatin (SS), its extremely short plasma half-life has inspired the synthesis of analogues with more favourable characteristics. The SS analogue octreotide contains the bioactive core of native molecule, consisting in an eight amino acid residue. Recent evidence has shown that the critical portion of any SS analogue is the D-Trp-Lys fragment. Presently, five specific human G protein-coupled SS receptor subtypes have been cloned and partially characterised. All five receptors bind native SS with high affinity, while octreotide binds with very high affinity only to subtype 2 (sst2) and shows moderately high affinity for sst5 and intermediate affinity for sst3.

High concentrations of sst2 receptors are expressed in numerous tumours, enabling primary and metastatic masses to be localised by scintigraphy after injection of indium-111 labelled octreotide, an SS analogue [1]. In addition to neuroendocrine tumours, SS receptors have been identified on cancers of the central nervous system [2], breast [3], lung and lymphatic tissue [4], and the use of radionuclide-labelled SS analogues shows promise for therapy as well as diagnosis of such cancers [5]. Moreover, sst2 receptors have been observed in peritumoural

vessels [6, 7], thus enabling an anti-angiogenetic response during radionuclide therapy.

Ongoing multicentre clinical trials, using high doses of ^{111}In-DTPA-octreotide (Octreoscan) in patients with neuroendocrine tumours [8], have yielded an objective response rate of approximately 15%, with a 66% overall response rate. These results may be ascribed to the Auger and conversion electrons emitted by ^{111}In. However, yttrium-90 seems more suitable for therapeutic use because of its energetic β-particles (E_{max}=2.27 MeV) and its long range [R_{95}=5.94 mm (R_{95} being the distance within which the β-particle transfers 95% of its energy to the target tissue)], which allows "cross-fire" irradiation.

Because of the low stability of ^{90}Y-DTPA linkage, the SS analogue [1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetra-acetic acid^0, D-Phe^1-Tyr^3]-octreotide (DOTATOC) was synthesised for stable labelling with ^{90}Y. DOTATOC has favourable characteristics for potential therapeutic use [9], in that it shows high affinity for sst2 [10, 11] and moderately high affinity for sst5, high hydrophilicity, and stable and easy labelling with ^{111}In and ^{90}Y [12, 13].

Following a previous biokinetics and dosimetry study in which ^{111}In-DOTATOC was administered to estimate absorbed doses during ^{90}Y-DOTATOC therapy [14, 15], we now report on the toxicity and therapeutic efficacy of ^{90}Y-DOTATOC in 30 patients with cancers expressing sst2.

Materials and methods

Patient population and inclusion criteria. We recruited 30 adult patients (18 men and 12 women; age 35–73 years) with histologically confirmed cancer (23 carcinoids, one breast cancer, three medullary thyroid cancers, one meningioma, one grade III astrocytoma and one small cell lung cancer) and documented residual disease or recurrence after conventional treatment. The main inclusion criterion was presence of SS receptors as documented by scintigraphy with ^{111}In-DOTATOC. Extension of disease was assessed by computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound. No chemotherapy or radiotherapy was given for at least 1 month before and 2 months after receptor-mediated radiotherapy (RMRT) with ^{90}Y-DOTATOC. Patient characteristics are shown in Table 1. Exclusion criteria were: (a) pregnancy or lactation; (b) age <21 years; (c) Karnofsky performance status <60 and life expectancy <6 months; (d) presence of a known second neoplasm; (e) white blood cell count <2,500/dl, haemoglobin <10 g/dl, platelets <100,000/dl, bilirubin >2.5 mg/dl, and (f) blood urea nitrogen (BUN) >45 mg/dl and creatinine >1.5 mg/dl. The study was performed at the European Institute of Oncology after approval by the Institute's Ethics Committee. All patients were informed of the nature, aim and potential risks of the study, and signed a consent form before beginning treatment.

Reagents. The SS analogue DOTATOC (DOTA: 1,4,7,10-tetraazacyclododecane-*N*,*N*',*N*'',*N*'''-tetra-acetic acid) was synthesised at the Division of Radiological Chemistry University Hospital, Basel according to a published procedure [13]. ^{90}Y chloride was purchased from AEA Technology (Harwell, UK). Typically, to 30 µg of DOTATOC in 30 µl 0.2 *M* ammonium acetate (pH 5.0) were added 150 µl of 0.4 *M* ammonium acetate/gentisic acid (pH 5.0) and 1.11 GBq $^{90}YCl_3$ in 0.04 *M* HCl. The mixture was then heated for 25 min at 90°C. Quality control of ^{90}Y-DOTATOC employed high-performance liquid chromatography and a Sep-Pak C18 cartridge (Waters, Millipore, Mass., USA), as previously described [16]. Labelling yields of more than 98% were routinely achieved at a specific activity of more than 50 GBq/µmol. A competition binding assay, using rat cortex membranes and [^{125}I-Tyr^3]octreotide as specific ligand [13], showed that the receptor binding affinity of the radiolabelled DOTATOC was preserved (K_D=2.2±0.5 n*M*).

Administration protocol. ^{90}Y-DOTATOC was injected intravenously over 20 min in 100 ml of physiological saline. A horizontal protocol was used: three equivalent activity doses were administered to each patient with an interval of 8 weeks between each. The first six patients received 30 µg of DOTATOC labelled with 1.11 GBq of ^{90}Y in each of three cycles over 6 months. The second group of six patients received 40 µg of DOTATOC labelled with 1.48 GBq of ^{90}Y for the same number of cycles. Major toxicity was not observed in these two groups, so the other three groups received 50, 60 and 70 µg of DOTATOC labelled with 1.85, 2.22 and 2.59 GBq of ^{90}Y, respectively. The patients were hospitalised for 2–3 days after treatment in rooms set aside for radionuclide therapy, and were discharged only after the level of activity in the urine had fallen below 0.037 MBq/ml.

Biodistribution and dosimetry. All patients received an ^{111}In-DOTATOC diagnostic scan before therapy and dosimetry was performed as previously described [14, 17]. In ten patients whose tumour mass (18 lesions) could be accurately evaluated by CT or MRI, whole body imaging was performed at 30 min, 3–4 h, 24 h and 48 h after injection using a double-head gamma camera (GE MAXXUS) equipped with a medium-energy general-purpose collimator. Single-photon emission tomography scans over the lesions were also obtained 3–4 h after injection and visually matched with the CT and MRI scans.

Regions of interest were drawn manually over the total body, tumour and normal organs, i.e. heart, lungs, liver, spleen and kidneys. Data from the gamma camera were converted to biological time-activity curves [$\%IA_{biol}(t)$] taking into account background, attenuation and physical decay. The SAAM II program was used to fit the observed kinetic data to a compartmental model [18]. After an acceptable fit had been obtained, the program was used to determine the residence times for ^{111}In and ^{90}Y in the source organs, assuming that the kinetics of ^{111}In- and ^{90}Y-labelled DOTATOC were identical [14, 19].

Dose calculations were performed according to the MIRD formalism, by entering the residence times for all source organs in the MIRDOSE 3.1 software and selecting the standard male or female phantom, as appropriate to the sex of each patient, so as to reduce the approximation resulting from considering standard organs [20].

All patients were also scanned at 24 and 48 h after the therapeutic dose of ^{90}Y-DOTADOC (bremsstrahlung imaging).

Safety and therapeutic effect. Toxicity was evaluated according to WHO criteria [21]. After discharge the patients underwent the following tests: renal function, hepatic function, lactate dehydrogenase and uricaemia every 15 days, and complete blood count 3 days after therapy and then weekly for the first 2 months. Tumour markers [5-hydroxyindoleacetic acid (5-HIAA), chromogranin A and others] were assayed 1 day before and 2 days after therapy and once a month for the following 2 months.

Objective therapeutic response was assessed by CT, MRI or both, with and without contrast, 6–8 weeks after the third cycle

Table 1. Summary of patient characteristics

Patient no.	Sex	Age (yrs)	Primary tumour	Lesions documented before ^{90}Y-DOTATOC therapy	Previous therapies	Total activity injected (GBq)
1	F	64	Bronchial carcinoid	Liver, bone	S	3.33
2	M	51	Ileal carcinoid	Liver	S, CT	3.33
3	F	47	Duodenal neuroendocrine tumour	Liver, peritoneum	S, CT	3.33
4	M	59	Pancreatic neuroendocrine tumour	Liver	S	3.33
5	M	61	Retroperitoneal neuroendocrine tumour	Retroperitoneum	S	3.33
6	F	63	Ileal carcinoid	Liver	S, TACE, SS analogues	3.33
7	M	58	Colonic carcinoid	Liver	S, TACE	4.44
8	M	50	Ileal carcinoid	Liver	S, TACE	4.44
9	F	46	Pancreatic neuroendocrine tumour	Liver, spleen, skin	CT	4.44
10	M	59	Bronchial carcinoid	Liver, lung	S, MIBG, SS analogues	4.44
11	M	49	Neuroendocrine tumour of unknown primary site	Liver	TACE	4.44
12	F	57	Neuroendocrine tumour of unknown primary site	Liver	TACE, MIBG, SS analogues	4.44
13	M	64	Medullary thyroid cancer	Bone, lymph nodes	S, RT	5.55
14	M	54	Pancreatic neuroendocrine tumour	Liver	S	5.55
15	F	55	Medullary thyroid cancer	Local recurrence	S	5.55
16	M	68	Ileal carcinoid	Liver, bone	S, CT	5.55
17	F	34	Medullary thyroid cancer	Thyroid, liver, bone, lymph nodes	S, RT	5.55
18	M	39	Rectal carcinoid	Bone	S	5.55
19	M	73	Ileal carcinoid	Liver	S	6.66
20	F	68	Pancreatic neuroendocrine tumour	Pancreas, liver	S	6.66
21	M	55	Meningioma	Brain	S, RT	6.66
22	F	40	Meningioma	Brain	S, RT	6.66
23	M	47	Pancreatic neuroendocrine tumour	Pancreas	S, IFN, CT	6.66
24	F	61	Neuroendocrine tumour of unknown primary site	Lung, liver, bone	S, SS analogues	6.66
25	M	47	Pancreatic neuroendocrine tumour	Pancreas, liver, bone, skin	None	7.77
26	M	49	Small cell lung cancer	Lung	S, RT	7.77
27	F	40	Breast cancer	Brain	S, CT, RT	7.77
28	M	50	Bronchial carcinoid	Liver, lung	S, CT	7.77
29	F	52	Carcinoid of unknown primary site	Liver	TACE	7.77
30	M	61	Jejunal carcinoid	Liver, lymph nodes, peritoneum	S	7.77

F, Female; M, male; S, surgery; CT, chemotherapy; TACE, transarterial chemoembolisation; MIBG, metaiodobenzylguanidine; RT, radiotherapy; IFN, interferon-α; SS, somatostatin

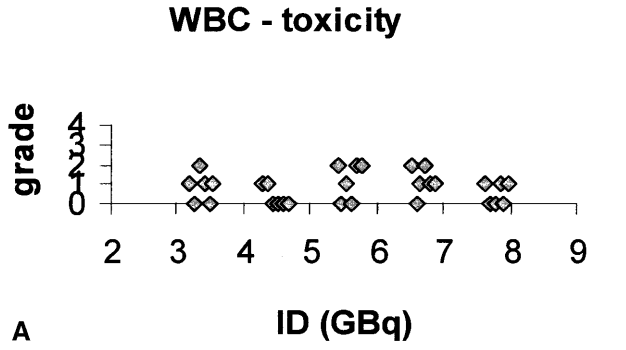
and then every 3 months. Tumour volumes were estimated by three independent observers, who examined the projections showing the most extensive tumour area, the maximum diameter and the corresponding perpendicular diameter. Hypodense and central hypointense areas, as well as changes revealed by contrast enhancement, were also assessed. It is to be noted, however, that response was defined according to WHO criteria as follows: complete response (CR) = total regression of all known lesions for at least 1 month; partial response (PR) = regression of all known lesions by more than 50%; minor response (MR) = regression of all known lesions by 25%–50%; stable disease (SD) = no change in lesion size; progressive disease (PD) = increase of all known lesions by 25% or more.

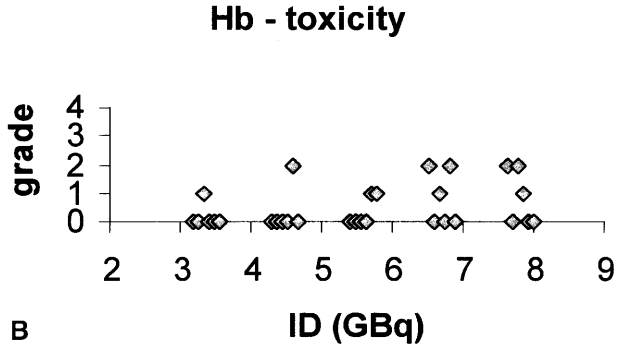
Tumour-related symptoms, namely presence and frequency of pain, diarrhoea, cutaneous flushing and consumption of symptomatic medication, were assessed monthly. Amelioration of symptoms and reduction in the level of tumour marker were interpreted as clinical benefit and not objective response.

Results

Biodistribution and dosimetry

The kinetics of ^{111}In-DOTATOC were used to calculate residence times for ^{90}Y-DOTATOC. The highest ab-





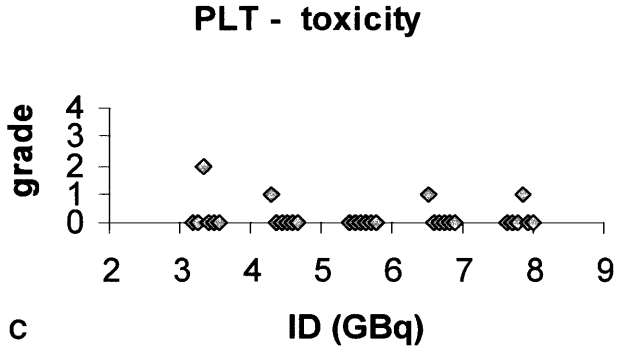


Fig. 1A–C. Haematological toxicity. **A** White blood cells; **B** haemoglobin; **C** platelets. Each *spot* represents a patient. The highest grade of toxicity reached after a single cycle and/or total dose is reported

sorbed doses were to spleen (7.6±6.3 mGy/MBq) and kidneys (3.3±2.2 mGy/MBq). The estimated absorbed dose to marrow was 0.03±0.01 mGy/MBq. The absorbed dose to other tissues was approximately 0.08± 0.04 mGy/MBq; the total body dose was 0.14± 0.06 mGy/MBq. The mean tumour residence time τ of ^{111}In-DOTATOC was 0.5 h (range 0.05–6.5 h). Based on these data, tumours were estimated to receive a mean dose of between 33 and 77 Gy for a cumulative injected activity ranging from 3.33 to 7.77 GBq. At this total of injected activity, kidneys received a mean dose of between 11 and 25 Gy. Thus a total injectable activity

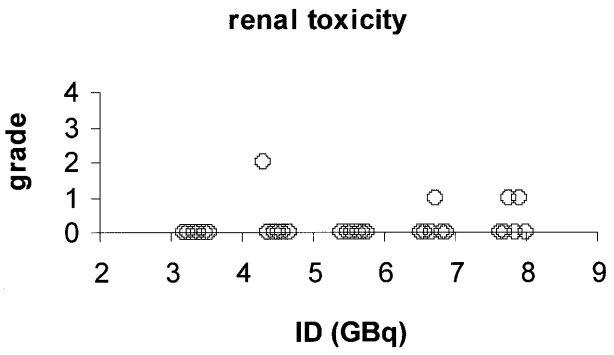


Fig. 2. Renal toxicity. Each *spot* represents a patient. The highest grade of toxicity reached after a single cycle and/or total dose is reported

based on a 25-Gy limit dose to the kidney was established [22].

Biodistribution was also checked after ^{90}Y-DOTATOC injection. Bremsstrahlung images were qualitatively compared with ^{111}In-DOTATOC pre-therapeutic diagnostic scan in order to verify the possible differences and to store useful data for further studies. Generally, good matching among the studies was recorded.

Toxicity

No major acute undesirable reactions were observed after ^{90}Y-DOTATOC injection up to 2.59 GBq per cycle, although five patients (16%) had moderate gastrointestinal toxicity: four grade 2 nausea (intake decreased but able to eat) and one grade 1 vomiting (one episode in 24 h). No other clinical manifestation of acute toxicity, such as skin reaction, allergy or fever, was observed. Major haematological toxicity (grade 3 or 4) did not occur (Fig. 1), except for a transient reduction in lymphocytes (grade 3 or 4 in almost all patients). No correlation was observed between administered dose and severity of lymphocytopenia, and recovery to pre-treatment levels occurred in all patients. Up to 5.55 GBq, most patients had haematological toxicity in the 0–1 range. Among those who received a cumulative dose in the range 6.66–7.77 GBq, 41.7% developed grade 2 toxicity after 3–4 weeks, but in all cases recovered in 4–6 weeks. These figures are as expected from the very low dose to marrow as estimated from the dosimetry study.

The renal toxicity after three treatments in patients who received cumulative doses in the range 3.33–7.77 GBq is shown in Fig. 2. Among these, none developed acute renal toxicity; however, three patients developed delayed grade 1 toxicity at a dose of 6.66–7.77 GBq. One patient, a 58-year-old man who had suffered from hypertension for 6 years, developed grade 2 renal toxicity 6 months after therapy. He received three cycles of 1.11 GBq for a cumulative dose of 3.33 GBq. The estimated kidney dose was 12 Gy. A year later creat-

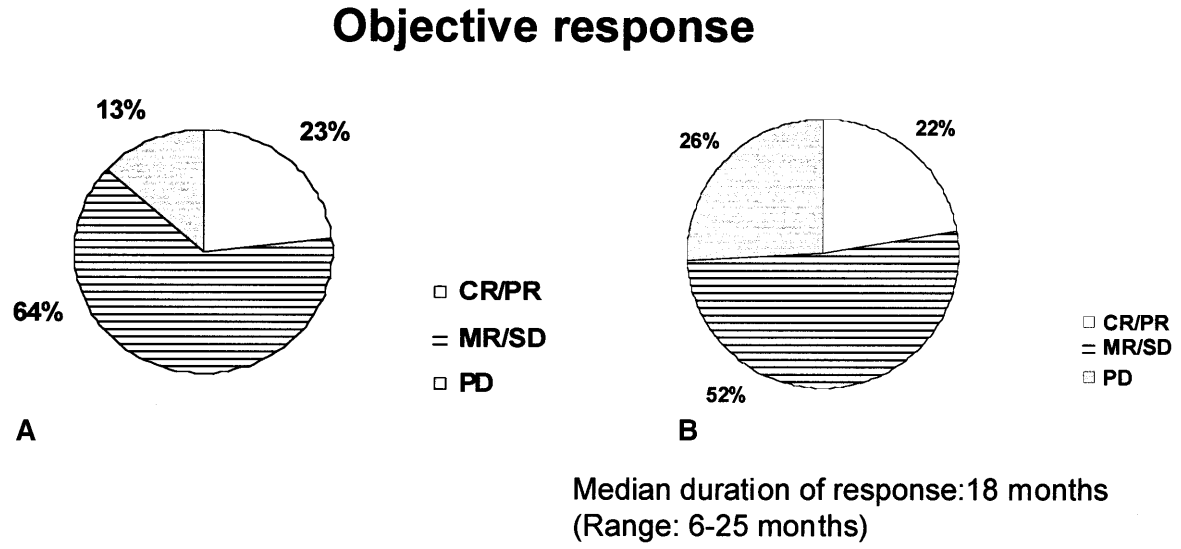


Fig. 3A, B. Summary of results after therapy with ^{90}Y-DOTATOC. **A** First check-up 2–4 months after completion of three cycles of therapy. **B** Latest check-up, 6–25 months after completion of therapy

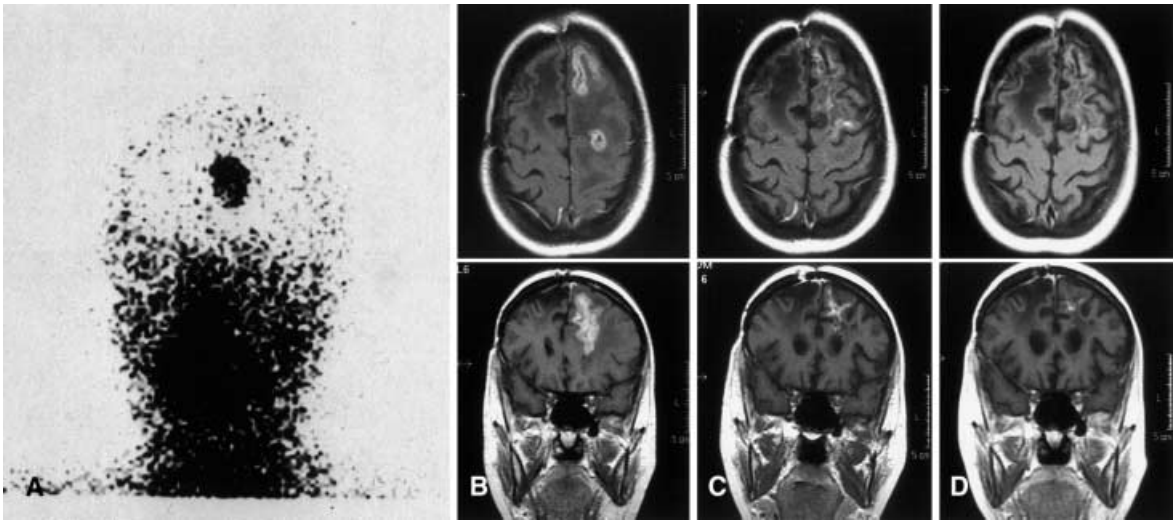


Fig. 4. A Pre-therapy planar head scan with ^{111}In-DOTATOC, showing uptake by tumour. **B–D** MRI scans before and after ^{90}Y-DOTATOC therapy. **B** MRI appearance before therapy. **C** Partial remission is seen 2 months after the second cycle of ^{90}Y-DOTATOC therapy. **D** Ten months after ^{90}Y-DOTATOC therapy, complete tumour regression is observed

inine and BUN had returned to normal, but the glomerular filtration rate, as detected by renal technetium-99m diethylene triamine penta-acetic acid scintigraphy, was reduced (data not shown).

Therapeutic effect

Figure 3A shows the overall results 2–4 months after therapy. Four patients (13.3%) did not respond to therapy (PD), 19 (63.3%) had stable disease and seven (23.3%) had tumour regression (CR/PR or MR). Figure 3B summarises the results at the latest check-up, 6–25 months after completion of therapy. At that time, 22% of patients were still responding to the therapy. Median duration of response was 18 months (range 6–25 months); follow-up continues. Examples of objective response are shown in Figs. 4 and 5. Figure 4B shows the MRI scan before therapy in a woman with brain metastasis from breast carcinoma (patient 27). The primary breast cancer (T3N1M0 ductal infiltrating carcinoma) was removed surgically in 1993 and this was followed by chemotherapy. In 1997 the patient received surgery and external radiotherapy for brain metastasis. In 1998 two new brain lesions, positive on ^{111}In-DOTATOC, were identified. She entered this study and received three cycles of 2.22 GBq, following which the lesions disappeared (Fig. 4D). Partial remission was observed after the second cycle (Fig. 4C). The CR has lasted 16 months, with

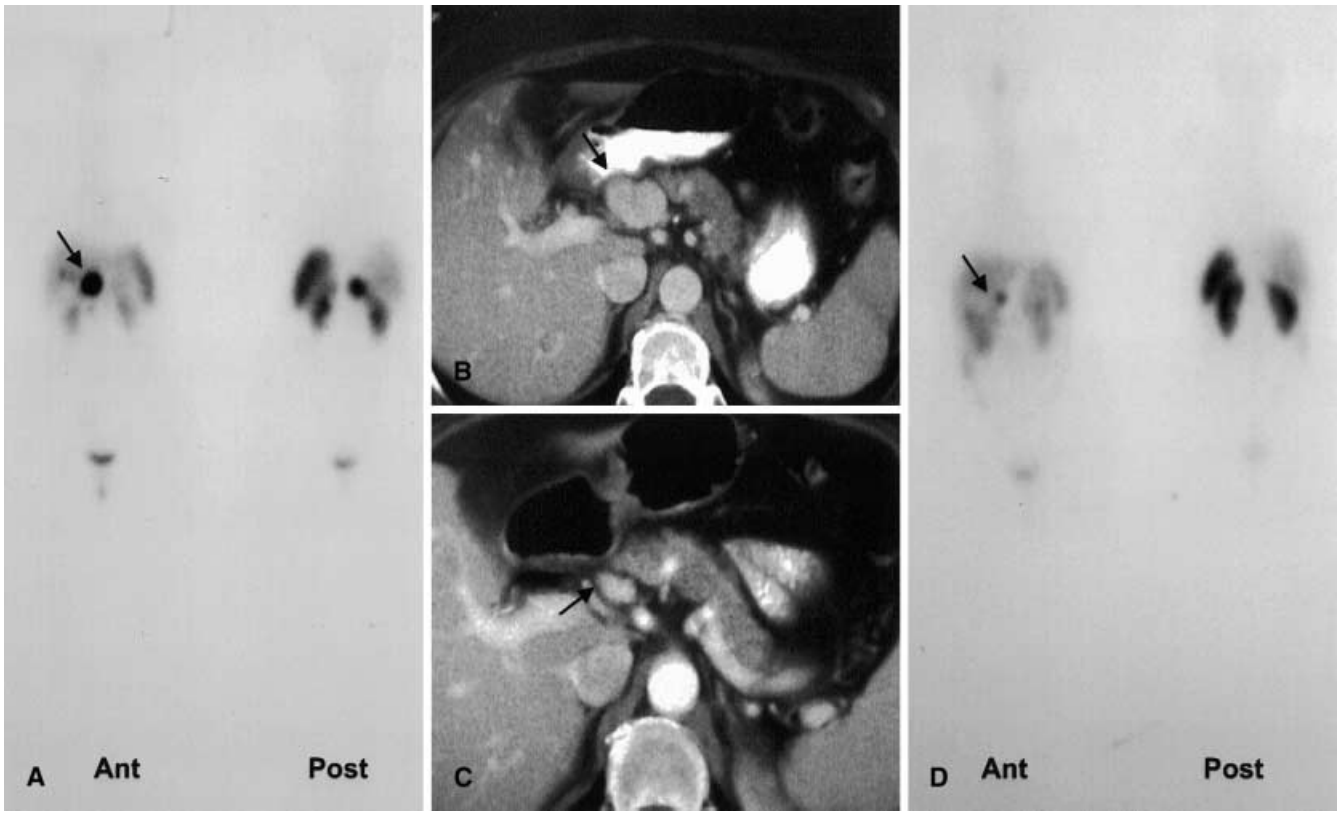


Fig. 5A–D. Patient with pancreatic carcinoid. **A** Whole body scan with ^{111}In-DOTATOC prior to therapy. Note strong uptake at tumour site (*arrow*). **B** Baseline CT showing a 3-cm pancreatic lesion. **C** CT scan 3 months after the end of the third cycle, showing partial remission. **D** Whole body scan after ^{111}In-DOTATOC administration at the end of therapy. Note greatly reduced uptake at the tumour site (*arrow*)

the patient still in remission at the most recent check-up (June 2000).

A good example of an objective PR is shown in Fig. 5. In this patient with carcinoid of the pancreatic head, tracer uptake was intense prior to therapy (Fig. 5A, whole body scan), while the biodistribution was excellent, with faint uptake in the rest of the body, including the kidneys. The patient received three doses of 2.59 GBq without evidence of toxicity. Subsequent CT (Fig. 5C in comparison to Fig. 5B) and ^{111}In control scans (Fig. 5D) showed a reduction in tumour mass of more than 80%. The carcinoid syndrome disappeared after the first cycle and the patient later gained weight. The duration of PR has been 15 months, and the patient was still in remission at latest check-up (May 2000).

Liver lesions from neuroendocrine tumours presented various findings on helical CT scan in our series. In particular, contrast enhancement and lesion dimensions during treatment did not behave uniformly; for this reason, follow-up included tumour marker assays and ^{111}In-DOTATOC scans as well as CT.

In 11 cases (36%) there was a mismatch between objective and humoural response. In these patients, all with neuroendocrine tumours, ^{111}In-DOTATOC uptake and marker levels reduced and there was a subjective improvement in symptoms and quality of life, although a less than 25% reduction in tumour size was seen on CT. By contrast, in two other cases (one small bowel carcinoid and one glucagonoma) CT showed CR of liver lesions with normalisation of urine 5-HIAA and serum glucagon, despite the fact that a control study with ^{111}In-DOTATOC still showed a small focus of tracer uptake at the tumour site (Fig. 6).

Discussion

The first finding of this study we wish to emphasise is that high doses of ^{90}Y-DOTATOC can be administered without myelotoxicity and with generally mild side-effects. For this reason, and as predicted by the dosimetric calculation, the maximum tolerated dose (MTD) of bone marrow per cycle has not yet been determined. Our dosimetric estimations suggest that it will probably be in the range of 5.5–6.7 GBq in patients of 70–80 kg.

Assuming the same biodistribution for the ^{111}In and ^{90}Y compounds, the predicted absorbed dose after administration of 3.7 GBq of ^{90}Y-DOTATOC is 12.2± 8.1 Gy for kidneys, 28.1±23.3 Gy for spleen and only 0.1±0.04 Gy for red marrow. Therefore, kidneys and spleen are likely to be the dose-limiting organs in pa-

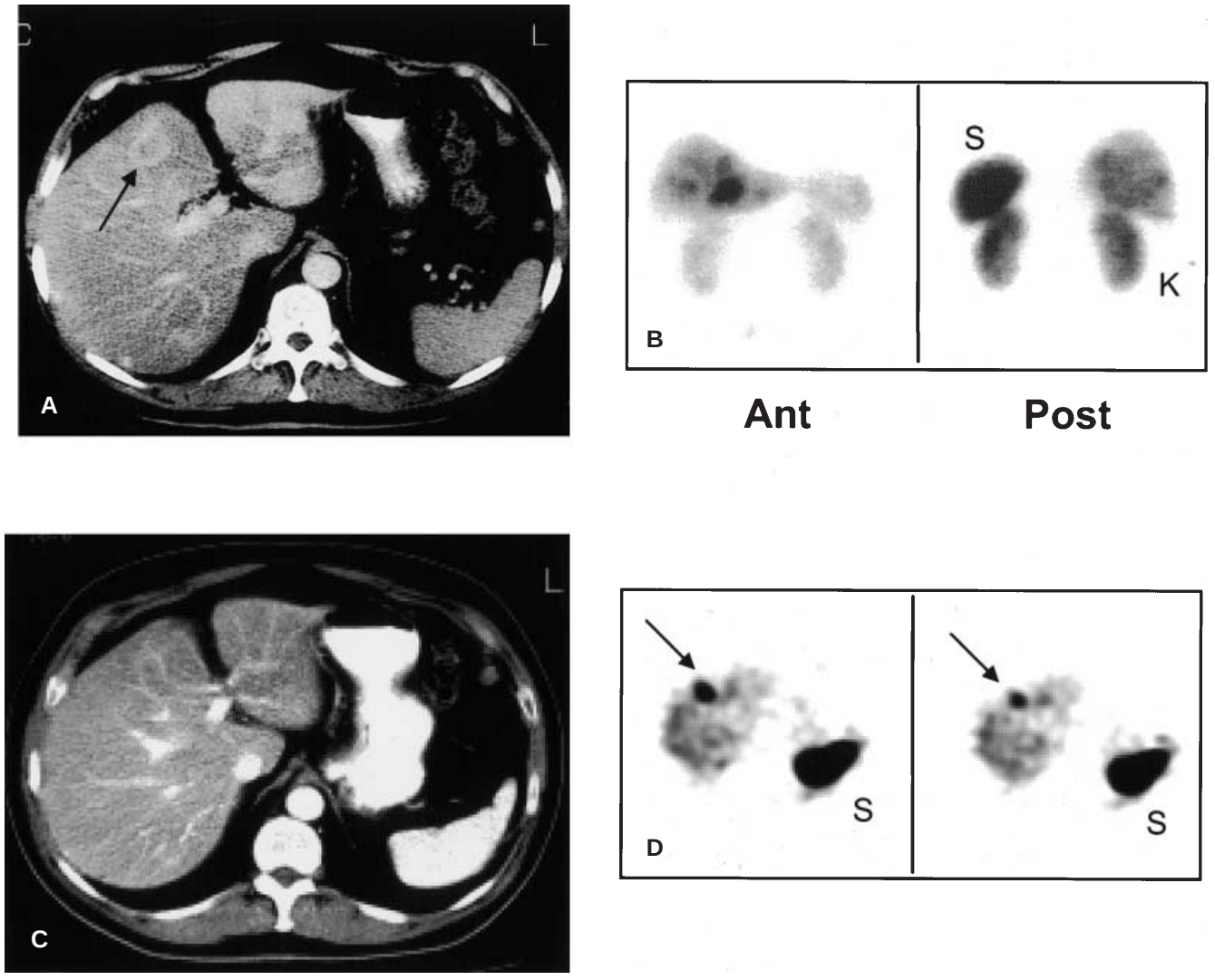


Fig. 6. **A** CT before treatment, showing a liver metastasis (*arrows*). **B** Pre-therapy ^{111}In-DOTATOC abdominal scan. **C** CT after treatment: the liver lesion is no longer visible. **D** Post-treatment ^{111}In-DOTATOC transaxial scan: pathological uptake is still evident in the 8th segment of the liver. *K*, Kidney; *S*, spleen

tients treated with repeated injections of ^{90}Y-DOTATOC, and although no major toxic effects have yet been observed in any organ, our main concern with this treatment is the cumulative effect of three cycles or more on the kidneys.

Due to the high concentration of sst2, a very high dose is delivered to the spleen (30–60 Gy/3.7–7.4 GBq). This is likely to cause splenic atrophy, which will increase the risk of septic shock by about 10% [23]. However, the likely benefit in terms of tumour regression, particularly when the ^{90}Y-DOTATOC therapy is combined with preventive anti-pneumococcal vaccination, may justify the risk to this organ. In our patients ^{111}In-DOTATOC control 4–6 months after ^{90}Y therapy showed normal spleen uptake, indicating that at the doses so far employed, no splenic atrophy occurs.

Possible reasons for the transient lymphocytopenia are the heterogeneity of expression of somatostatin receptors in lymphoid tissue (which seems to be dependent on the activation state of the cells and on their homing or circulating condition) and the variable modulatory functions exerted by somatostatin on immune cells [24, 25].

The renal tolerated dose having a 5% probability of late toxicity within 5 years (TD 5/5) has been estimated at 20–25 Gy when external irradiation is delivered to both kidneys over 3–5 weeks using reduced daily fractions [22]. Internal delivery of radionuclides, by RMRT for example, might be less toxic than conventional external radiotherapy, as this kind of radiotherapy is characterised by a continuous decrease in dose rate. We may therefore be justified in escalating doses to a higher level. However, we decided to comply with the external radiotherapy model of renal tolerance, considering also that late toxic effects on the kidneys may not manifest for several years [26, 27]. Follow-up of the present series should provide useful data on late effects on the kidneys after ^{90}Y-DOTATOC therapy at the 20–25 Gy level.

Table 2. Summary of the latest follow-up data for all patients

Patient no.	Total activity (GBq)	Creatinine (mg/dl)	BUN (mg/dl)	Last follow-up (months after therapy)[a]	Status at latest follow-up
1	3.33	0.8	39	25	SD
2	3.33	2.9	38	24	PR
3	3.33	0.9	41	17	PR
4	3.33	0.9	48	20	SD
5	3.33	1.5	65	19	SD
6	3.33	0.7	42	19	PD
7	4.44	3	104	24	SD
8	4.44	1	39	20	PR
9	4.44	0.7	31	18	PD
10	4.44	1	17	14	PD
11	4.44	0.9	34	6	–[b]
12	4.44	0.8	47	22	SD
13	5.55	1.03	30	12	SD
14	5.55	0.9	45	12	CR
15	5.55	0.9	44	12	SD
16	5.55	1.02	57	3	–[c]
17	5.55	0.9	31	10	SD
18	5.55	1.15	25	19	SD
19	6.66	1.4	43	13	SD
20	6.66	0.7	18	20	MR
21	6.66	1.02	29	22	SD
22	6.66	1.07	20	6	PD
23	6.66	0.9	15	10	PD
24	6.66	1.07	38	11	PD
25	7.77	0.9	34	7	–[d]
26	7.77	1	28	6	PD
27	7.77	0.6	30	16	CR
28	7.77	0.9	23	10	PD
29	7.77	1.1	44	15	PR
30	7.77	1.15	34	6	SD

BUN, Blood urea nitrogen; CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease (for precise definition of response, see Materials and methods)

[a] Median 14.5 (range 3–25)

[b] Patient lost in follow-up

[c] Died because of acute myocardial infarction

[d] Died because of disease progression

Only one patient developed late grade 2 renal toxicity (in the group that received 3.33 GBq). This was probably due to impaired baseline renal function as a result of chronic hypertension, although creatinine levels in serum were in the normal range prior to therapy. At the latest check-up, 22 months after therapy, BUN was again in the normal range after only dietary therapy, and the patient is still in remission from the liver lesions. The latest follow-up data for all patients are shown in Table 2.

The administration of amino acids to reduce renal uptake is being explored [28, 29, 30]. Animal studies have shown a significant reduction (50%–60%) in renal uptake after intravenous administration of D-lysine, with no effect on blood clearance or tumour uptake. If renal protection allows injection of about 50% more activity, the total injectable activity will be increased to about 11–13 GBq. This respects the 20–25 Gy tolerance dose limit for kidneys [22], which must be adhered to unless long follow-up demonstrates that there is no late renal toxicity at the doses already employed.

The question as to the best mode of administering the activity remains. We administered a sequence of equivalent doses at intervals long enough apart to reveal acute and sub-acute toxicity. It is unclear whether a single cycle of the highest injectable dose or a multiple low-dose regimen provides the best response, although we found no relation between injected activity and response rate in the present series.

We observed objective responses (CR or PR) in 23.3% of patients while 63.3% had MR or SD with subjective improvement and reduced levels of tumour markers. In all cases, tumour uptake was high and showed a sufficiently long residence time, suggesting that this new compound is suitable for receptor-mediated radiotherapy. Tumour residence times varied widely (0.05–6.5 h), giving absorbed doses in a range of 1.4–31.0 mGy/MBq with a mean value of 10.1 mGy/MBq; this corresponds to a mean total dose of 33 or 77 Gy after the administration of 3.3 or 7.7 GBq, respectively. The observed variation may be due to factors such as tumour volume, interstitial pressure, vascularisation and receptor density on the tumour.

Another point to be addressed is when this therapy should be given and to whom. We believe that our preliminary results justify recruitment of patients with minimal residual disease and favourable biodistribution, although traditional chemo- and radiotherapeutic approaches should be integrated.

In conclusion, this study shows that it is possible to deliver high doses of radioactivity to tumour by administration of ^{90}Y-DOTATOC and that objective therapeutic responses are achieved in close to a quarter of patients. Methods being developed to reduce renal uptake (i.e. amino acid infusion) will probably make it possible to considerably decrease the absorbed dose to this critical organ while increasing the tumour dose. A study is required to clarify this and to determine the MTD per cycle with renal amino acid protection.

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