# Treatment with $^{177}$Lu-DOTATOC of Patients with Relapse of Neuroendocrine Tumors After Treatment with $^{90}$Y-DOTATOC

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Therapy with [$^{90}$Y-DOTA$^0$, Tyr$^3$]-octreotide (DOTATOC, where DOTA = tetraazacyclododecane tetraacetic acid and TOC = D-Phe-c(Cys-Tyr-D-Trp-Lys-Thr-Cys)-Thr(ol)) is established for the treatment of metastatic neuroendocrine tumors. Nevertheless, many patients experience disease relapse, and further treatment may cause renal failure. Trials with $^{177}$Lu-labeled somatostatin analogs showed less nephrotoxicity. We initiated a prospective study with $^{177}$Lu-DOTATOC in patients with relapsed neuroendocrine tumors after $^{90}$Y-DOTATOC treatment. **Methods:** Twenty-seven patients, pretreated with $^{90}$Y-DOTATOC, were included. The mean time between the last treatment with $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATOC was 15.4 ± 7.8 mo (SD). All patients were injected with 7,400 MBq of $^{177}$Lu-DOTATOC. Restaging was performed after 8–12 wk. Hematotoxicity or renal toxicity of World Health Organization grade 1 or 2 was not an exclusion criterion. **Results:** Creatinine levels increased significantly, from 66 ± 14 μmol/L to 100 ± 44 μmol/L ($P < 0.0001$), after $^{90}$Y-DOTATOC therapy. The mean hemoglobin level dropped from 131 ± 14 to 117 ± 13 g/L ($P < 0.0001$) after $^{90}$Y-DOTATOC therapy. $^{177}$Lu-DOTATOC therapy was well tolerated. No serious adverse events occurred. The mean absorbed doses were 413 ± 159 mGy for the whole body, 3.1 ± 1.5 Gy for the kidneys, and 61 ± 5 mGy for the red marrow. After restaging, we found a partial remission in 2 patients, a minor response in 5 patients, stable disease in 12 patients, and progressive disease in 8 patients. Mean hemoglobin and creatinine levels did not change significantly. **Conclusion:** $^{177}$Lu-DOTATOC therapy in patients with relapse after $^{90}$Y-DOTATOC treatment is feasible, safe, and efficacious. No serious adverse events occurred.

**Key Words:** $^{177}$Lu-DOTATOC; $^{90}$Y-DOTATOC; radionuclide therapy; somatostatin; neuroendocrine tumors

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Treatment options for metastatic neuroendocrine tumors are limited. Trials with long-acting somatostatin analogs (octreotide or lanreotide), interferon-α, or chemotherapy, mostly 5-fluorouracil based, have shown rather low response rates with regard to cytoreduction (*1–3*). However, somatostatin analogs inhibit flushing, diarrhea, and other symptoms of the carcinoid syndrome (*4,5*). A retrospective case series in 1996 suggested that survival has increased since the introduction of somatostatin analogs (*6*). In the last few years, treatment strategies with radiolabeled somatostatin analogs have shown more convincing results (*7–13*). The 3 most investigated radiopharmaceuticals in clinical trials are [$^{111}$In-diethylenetriaminepentaacetic acid (DTPA)$^0$]-octreotide, [$^{90}$Y-DOTA$^0$, Tyr$^3$]-octreotide (DOTATOC, where DOTA = tetraazacyclododecane tetraacetic acid and TOC = D-Phe-c(Cys-Tyr-D-Trp-Lys-Thr-Cys)-Thr(ol)), and [$^{177}$Lu-DOTA$^0$, Tyr$^3$, Thr$^8$]-octreotide (DOTATATE) (*7–13*).

Initial studies with high activities of [$^{111}$In-DTPA$^0$]-octreotide were encouraging. Although partial remissions were not found, favorable effects on symptoms were reported. Many patients in poor clinical condition were included (*12,13*). For the other 2 radiopeptides, a high overall response rate and distinct improvement in quality of life could be demonstrated (*10,14*). Although the results with these radiolabeled somatostatin analogs seem promising, relapses occur after a certain time in many patients (*15*), and further treatment with $^{90}$Y-DOTATOC can cause renal failure (*16*). According to data in the literature, the median time to progression after treatment with $^{90}$Y-DOTATOC is 30 mo (*17,18*). For $^{177}$Lu-DOTATATE, the median time to progression had not been reached at 25 mo after the start of therapy (*19*).

In comparison to $^{90}$Y, which is a high-energy, pure β-emitter ($E_{max}$, 2.25 MeV), $^{177}$Lu is a low-energy β-emitter (maximum electron energy [$E_{max}$], 0.497 MeV) with a small γ-component that is suitable for scintigraphic imaging (133 keV [6.5%]; 208 keV [11%]) without using a radionuclide surrogate. Small peptides such as DOTATOC are reabsorbed by the proximal tubules of the kidneys (*20*). The

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damage that can occur after treatment with $^{90}$Y-DOTATOC is in the glomeruli. It is conceivable that the length of the β-particles influences kidney toxicity. This hypothesis is supported by animal experiments (*21*).

Renal toxicity has been identified as the dose-limiting factor of $^{90}$Y-DOTATOC therapy (*9*). In a study with [$^{177}$Lu-DOTA$^0$, Tyr$^3$, Thr$^8$]-octreotide, no nephrotoxicity was found (*11*). Although no long-term outcome data concerning nephrotoxicity after treatment with $^{90}$Y-DOTATOC or $^{177}$Lu-DOTATATE are available, we assumed that $^{177}$Lu might be less nephrotoxic than $^{90}$Y.

In vitro, a higher affinity to the somatostatin receptor subtype 2 was demonstrated for Y$^{(III)}$-DOTATATE than for Y$^{(III)}$-DOTATOC (*22*). However, because in humans a better tumor-to-kidney-ratio was found for $^{111}$In-DOTATOC than for $^{111}$In-DOTATATE (*23*), we decided to use DOTATOC as a DOTA-peptide conjugate labeled to $^{177}$Lu in patients with relapse.

We initiated a prospective feasibility study with $^{177}$Lu-DOTATOC in patients with relapse of neuroendocrine tumors after successful treatment with $^{90}$Y-DOTATOC. Because of the assumption that $^{177}$Lu-DOTATOC is less nephrotoxic than $^{90}$Y-DOTATOC, we did not consider World Health Organization (WHO) grade 1 or 2 renal toxicity, based on creatinine levels, to be an exclusion criterion, nor were patients with WHO grade 1 or 2 hematotoxicity excluded. Human data for $^{177}$Lu-DOTATATE show promising results and a tolerable toxicity for injected activities of around 22.2–29.6 GBq (600–800 mCi) in patients who are not pretreated with peptide receptor–mediated radionuclide therapy (*11*). But for $^{177}$Lu-DOTATOC, we could find no human data in the literature. Because our patients were pretreated with peptide receptor–mediated radionuclide therapy, and because no dosimetric data were available, we started with a relatively low injected activity. We treated all patients with a fixed activity of 7,400 MBq (200 mCi).

## MATERIALS AND METHODS

The study was approved by the local ethical committee and the Swiss authorities. All patients gave written informed consent.

### Patients

Twenty-seven patients (17 men and 10 women) were included. The mean age (± SD) was 58 ± 9 y. All patients had a histologically confirmed metastatic neuroendocrine tumor, which was progressive at the time of treatment. The progression was demonstrated by CT or ultrasound in all patients. All patients were pretreated with $^{90}$Y-DOTATOC and benefited from this treatment. Benefit was defined as complete remission, partial remission, minor response, or stable disease according to the WHO standard criteria. For the partial remissions in our collective, the mean time to progression was 15.4 ± 6.9 mo. Many patients were pretreated with surgery, chemotherapy, octreotide, or interferon as well. Details are listed in Table 1.

Pretherapeutically, all patients underwent staging with CT, $^{111}$In-pentetreotide scintigraphy (OctreoScan; Mallinckrodt, Inc.), complete blood counts, and blood chemistry. The findings of $^{111}$In-octreotide scintigraphy were strongly positive in all patients. None of the patients had been treated with the long-acting somatostatin analogs octreotide (Sandostatin LAR; Novartis) or lanreotide (Somatuline; Ipsen) during at least the last 6 wk before receiving $^{177}$Lu-DOTATOC or with short-acting octreotide (Sandostatin s.c.; Novartis) during the last 3 d before receiving $^{177}$Lu-DOTATOC.

### Radiotracer

DOTATOC was synthesized as previously described (*24*). For radiolabeling DOTATOC, we used lyophilized kits containing DOTATOC, gentisic acid, inositol, and sodium ascorbate (pH 5.0).

We added 7,400 MBq of $^{177}LuCl_3$ (IDB Holland BV) to the lyophilized DOTATOC kits and heated them for 30 min at 95°C. After they had been cooled to room temperature, a quality control check was performed using an analytic high-performance liquid chromatograph (model 1050; Hewlett Packard) with a radiometric detector (model LB 506 C1; Berthold). Additionally, the labeling yield was determined by separation of bound and free $^{177}Lu^{3+}$ using Sep-Pak C18 cartridges (Waters). After $^{177}$Lu-DOTATOC had been loaded onto the cartridge, the free $^{177}$Lu was eluted with sodium acetate buffer (0.4 mol/L, pH 5.0), and bound $^{177}$Lu-DOTATOC was then eluted with methanol. Each fraction was measured on a γ-counter.

### Treatment

The patients were hospitalized for 3 d in accordance with the legal requirements for radioactivity control. A single, fixed-activity treatment protocol was used. The injected activity was 7,400 MBq of $^{177}$Lu-DOTATOC. An infusion of 2,000 mL of an amino acid solution (Ringer's lactated Hartmann solution, Proteinsteril [B. Braun Medical AG] HEPA 8%, Mg 5-Sulfat [B. Braun Medical AG]) to inhibit tubular reabsorption of the radiopeptide was started 30 min before administration of the radiopharmaceutical and was continued until up to 3 h after administration of the radiopharmaceutical (*20,25,26*).

### Imaging and Dosimetry

Imaging was performed with a dual-head Prism 2000 XP camera (Picker) using parallel-hole, medium-energy, general-purpose collimators. The windows were centered over both $^{177}$Lu photon peaks (113 and 208 keV) with a window width of 20%. In 4 patients, whole-body scans for dosimetry were obtained immediately and at 4, 24, and 28 h after injection. The acquisition time for the whole-body scans was 15 min. In all other patients, whole-body scans and spot images were obtained after 24 and 28 h for control of biodistribution.

To determine blood clearance, we drew blood samples from 4 patients at 5, 10, 30, and 60 min and at 12, 4, 24, and 28 h after injection. Radioactivity in blood was measured with a γ-counter (Cobra II; Canberra-Packard).

For dosimetric calculations, regions of interest were drawn manually on the whole-body scans from anterior and posterior projections. Those parts of the kidneys showing tumor infiltration or superimposition were excluded from the evaluation of organ uptake. The Odyssey XP program (Philips Electronics N.V.) was used. Background regions were placed close to the regions of interest for background correction. The geometric mean value between anterior and posterior was taken and corrected for attenuation and physical decay. Whole-body activity acquired immediately after injection was defined as 100% of the injected activity.

**TABLE 1**
Patient Characteristics

| Patient no. | Sex | Age (y) | Diagnosis | Date of diagnosis | Classification 3 mo after $^{90}$Y-DOTATOC | Pretreatments (except $^{90}$Y-DOTATOC) | Number of $^{90}$Y-DOTATOC treatments | Total dose of $^{90}$Y-DOTATOC/m$^2$ | Months since last treatment with $^{90}$Y-DOTATOC |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 71 | Neuroendocrine tumor of small bowel | Nov 01 | Stable disease | — | 2 | 200 | 16 |
| 2 | M | 55 | Neuroendocrine tumor of pancreas | Jun 97 | Partial remission | S, Oct, Ch | 3 | 300 | 11 |
| 3 | M | 63 | Neuroendocrine tumor of pancreas | Dec 00 | Stable disease | Ch, INF | 2 | 200 | 18 |
| 4 | F | 74 | Neuroendocrine tumor of appendix | Jan 00 | Stable disease | S | 3 | 200 | 8 |
| 5 | F | 55 | Neuroendocrine tumor of pancreas | Feb 01 | Partial remission | S | 2 | 200 | 22 |
| 6 | F | 60 | Neuroendocrine tumor with unknown primary | Dec 99 | Partial remission | Oct | 2 | 200 | 16 |
| 7 | F | 59 | Neuroendocrine tumor of stomach | Nov 00 | Minor response | S | 3 | 300 | 10 |
| 8 | F | 51 | Neuroendocrine tumor of rectum | Aug 95 | Partial remission | S | 2 | 200 | 22 |
| 9 | M | 56 | Neuroendocrine tumor of small bowel | June 02 | Partial remission | Oct | 2 | 200 | 9 |
| 10 | M | 60 | Neuroendocrine tumor of small bowel | Mar 99 | Partial remission | S | 2 | 200 | 11 |
| 11 | F | 65 | Neuroendocrine tumor of pancreas | Dec 98 | Partial remission | Oct, INF | 2 | 200 | 10 |
| 12 | M | 38 | Neuroendocrine tumor with unknown primary | Mar 98 | Stable disease | Oct, Ch, $^{186}$Re-HEDP | 3 | 300 | 18 |
| 13 | M | 58 | Neuroendocrine tumor with unknown primary | May 01 | Minor response | S | 2 | 200 | 17 |
| 14 | M | 54 | Neuroendocrine tumor of small bowel | Oct 00 | Minor response | S | 2 | 200 | 24 |
| 15 | M | 63 | Neuroendocrine tumor of pancreas (insulinoma) | Sep 01 | Partial remission | Oct | 2 | 200 | 13 |
| 16 | M | 76 | Neuroendocrine tumor of pancreas | Nov 98 | Partial remission | S | 2 | 200 | 32 |
| 17 | M | 49 | Neuroendocrine tumor of pancreas | Dec 01 | Partial remission | Oct | 2 | 200 | 9 |
| 18 | M | 43 | Neuroendocrine tumor of pancreas | Feb 01 | Partial remission | S, Ch | 3 | 300 | 14 |
| 19 | F | 66 | Neuroendocrine tumor of pancreas | Aug 96 | Partial remission | S | 2 | 200 | 22 |
| 20 | M | 49 | Neuroendocrine tumor of rectum | Jun 00 | Partial remission | S, Oct, INF | 2 | 200 | 11 |
| 21 | F | 46 | Neuroendocrine tumor of unknown origin, most likely insulinoma | Jan 97 | Stable disease | Oct | 3 | 300 | 32 |
| 22 | M | 51 | Neuroendocrine tumor of small bowel | Apr 00 | Stable disease | S | 3 | 300 | 5 |
| 23 | M | 65 | Neuroendocrine tumor of small bowel | Feb 02 | Stable disease | S | 2 | 200 | 4 |
| 24 | F | 60 | Neuroendocrine tumor of small bowel | Oct 99 | Stable disease | S | 3 | 300 | 22 |
| 25 | M | 65 | Neuroendocrine tumor of bronchus | Mar 99 | Partial remission | Ch | 3 | 300 | 6 |
| 26 | M | 50 | Neuroendocrine tumor of pancreas | May 98 | Stable disease | S, Oct, INF, Ch | 2 | 200 | 27 |
| 27 | M | 51 | Neuroendocrine tumor of pancreas (gastrinoma) | Feb 00 | Stable disease | S | 2 | 200 | 8 |

S = surgery; Oct = octreotide (long- or short-acting) or lanreotide; Ch = chemotherapy; INF = interferon.

Data were expressed as percentage injected activity as a function of time. The resulting time–activity data were fitted to a monoexponential curve for the whole-body clearance and to a biexponential curve for the kidneys to calculate residence time. Published radiation dose factors were used to calculate the absorbed doses (*27*).

The activity in blood was fitted to a biexponential curve to determine the residence time in blood. The dose to the red marrow was calculated from the residence time in blood, assuming no specific uptake, a uniform distribution of activity, and clearance from red marrow equal to that from blood. A correction factor of 1 was used as described by Cremonesi et al. (*28*).

### Evaluation of Results and Assessment of Clinical Benefit

Pretherapeutically, patients underwent disease staging. Eight to 12 wk after peptide receptor–mediated radionuclide therapy, tumor growth and tumor response were monitored by CT or ultrasound. Tumor response was defined according to the WHO standard criteria. In addition, complete blood cell and platelet counts were obtained every 2 wk for at least 8 wk or until resolution of nadir. Side effects were scored according to the WHO criteria.

### Statistics

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

## RESULTS

The study included 27 patients with metastasized tumors, 11 of whom had neuroendocrine pancreatic tumors and 16, neuroendocrine tumors of other sites (7 of the small bowel, 4 of unknown primary, 2 of the rectum, 1 of the stomach, 1 of the bronchus, and 1 of the appendix). Detailed patient characteristics are listed in Table 1.

### Evaluation of Long-Term Outcome After $^{90}$Y-DOTATOC Therapy

All patients had progressive disease before $^{90}$Y-DOTATOC therapy and before $^{177}$Lu-DOTATOC therapy. One criterion for inclusion into this study was benefit from $^{90}$Y-DOTATOC therapy. Of the 27 patients studied, we found a partial remission in 14, a minor response in 3, and stable disease in 10 at 3 mo after the last treatment with $^{90}$Y-DOTATOC.

The mean time between the last treatment with $^{90}$Y-DOTATOC and the treatment with $^{177}$Lu-DOTATOC was 15.4 ± 7.8 mo (range, 4–32 mo).

Before therapy with $^{90}$Y-DOTATOC, the mean hemoglobin level was 131 ± 14 g/L, the mean thrombocyte level was 306 ± 123 × $10^9$/L, and the mean creatinine level was 66 ± 14 μmol/L. Before treatment with $^{177}$Lu-DOTATOC, the level of hemoglobin was significantly lower: 117 ± 13 g/L ($P < 0.0001$). The thrombocyte counts (263 ± 83 × $10^9$/L) were lower as well but did not show significant changes. Creatinine levels increased to 100 ± 44 μmol/L. The difference was significant ($P < 0.0001$), although a high SD was seen. Details are listed in Table 2.

### Labeling of $^{177}$Lu-DOTATOC

The quality control testing of $^{177}$Lu-DOTATOC was done using 2 independent systems; the labeling efficiency was determined by analytic high-performance liquid chromatography and ranged from 99% to 100%. When the labeling yield was less than 99.5%, DTPA (1 mmol/L, pH 7.4) was added.

### Dosimetry

Dosimetric calculations were performed on 4 patients and resulted in a mean whole-body absorbed dose of 413 ± 159 mGy. The mean absorbed dose to the kidney was 3.1 ± 1.5 Gy, and that to the red marrow was 61 ± 5 mGy.

### Treatment with $^{177}$Lu-DOTATOC

The treatment was well tolerated. No severe adverse events occurred. Nausea and vomiting within the first 24 h after treatment occurred in 8 patients (30%). All cases of nausea and vomiting could be treated successfully with domperidone and ondansetron. Some increase of pain at the site of the tumor was experienced by 5 patients (19%) within the first 48 h after treatment. All cases could be controlled with analgesics. No other nonhematologic toxicity was found.

As expected. $^{177}$Lu-DOTATOC showed a high specific uptake in somatostatin receptor–positive tumors. The γ-component of $^{177}$Lu allowed acquisition of scintigraphic images of a high level of quality (Fig. 1A).

At the time of restaging, we found no change in creatinine levels. With these findings, late nephrotoxicity cannot be excluded definitely. But if nephrotoxicity arises, an increase in creatinine levels has usually been found 3 mo after treatment (*16*). Before treatment, 9 patients had grade 1 anemia and 1 had grade 2. Eight to 12 wk after treatment, 8 patients had grade 1 anemia, 1 had grade 2, and 1 had grade 3. The mean level of thrombocytes decreased significantly, from 263 ± 82 to 197 ± 70 × $10^9$/L ($P < 0.01$). Details are listed in Table 2.

Eight to 12 wk after treatment, 8 patients did not show a benefit from peptide receptor–mediated radionuclide therapy and continued to have progressive disease. Nineteen patients (70%) showed a benefit: 12 with stabilization of the disease, 5 with a minor response, and 2 with partial remission. Scans of patient 9, with a minor response, are shown in Figure 1, and corresponding anatomic images are shown in Figure 2. According to the referring physicians, the general condition of the patients improved for 15 (56%), remained the same for 11 (41%), and decreased for only 1 (4%).

The subgroup of patients who achieved partial remission after $^{90}$Y-DOTATOC ($n = 14$) included 2 with partial remission, 5 with a minor response, and 7 with stable disease after $^{177}$Lu-DOTATOC treatment. In no patient of this subgroup did the disease remain progressive.

The overall time of follow-up was 4–17 mo (mean, 11.0 ± 4.0 mo). The time of remission (stable disease, minor response, or partial remission) ranged from 4 to 13

**TABLE 2**
Blood Values and Clinical Results

| Patient no. | Hemoglobin (g/L) | | | Thrombocytes ($\times 10^9$/L) | | | Creatinine (μmol/L) | | | Clinical result after treatment with $^{177}$Lu-DOTATOC |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before $^{90}$Y-DOTATOC treatment | Before $^{177}$Lu-DOTATOC treatment | After $^{177}$Lu-DOTATOC treatment | Before $^{90}$Y-DOTATOC treatment | Before $^{177}$Lu-DOTATOC treatment | After $^{177}$Lu-DOTATOC treatment | Before $^{90}$Y-DOTATOC treatment | Before $^{177}$Lu-DOTATOC treatment | After $^{177}$Lu-DOTATOC treatment | |
| 1 | 104 | 87 | 72 | 406 | 372 | 206 | 83 | 133 | 118 | Stable disease |
| 2 | 116 | 102 | 105 | 176 | 188 | 143 | 77 | 117 | 124 | Stable disease |
| 3 | 133 | 115 | 115 | 302 | 251 | 122 | 68 | 94 | 62 | Progressive disease |
| 4 | 116 | 115 | 108 | 285 | 188 | 200 | 60 | 111 | 75 | Progressive disease |
| 5 | 127 | 119 | 116 | 129 | 173 | 95 | 52 | 65 | 70 | Partial remission |
| 6 | 107 | 107 | 109 | 311 | 152 | 133 | 54 | 59 | 62 | Stable disease |
| 7 | 115 | 100 | 102 | 268 | 239 | 108 | 33 | 60 | 63 | Progressive disease |
| 8 | 133 | 116 | 115 | 218 | 303 | 190 | 45 | 58 | 43 | Minor response |
| 9 | 145 | 137 | 116 | 226 | 182 | 132 | 74 | 96 | 97 | Minor response |
| 10 | 135 | 134 | 115 | 218 | 214 | 329 | 61 | 58 | 68 | Minor response |
| 11 | 111 | 110 | 112 | 679 | 299 | 127 | 57 | 62 | 61 | Minor response |
| 12 | 136 | 123 | 128 | 227 | 462 | 252 | 61 | 84 | 82 | Stable disease |
| 13 | 126 | 127 | 112 | 275 | 234 | 208 | 71 | 88 | 84 | Progressive disease |
| 14 | 160 | 140 | 135 | 243 | 244 | 219 | 71 | 96 | 114 | Progressive disease |
| 15 | 110 | 105 | 80 | 348 | 187 | 109 | 65 | 197 | 167 | Partial remission |
| 16 | 141 | 109 | 104 | 241 | 282 | 241 | 70 | 137 | 112 | Stable disease |
| 17 | 146 | 131 | 130 | 279 | 245 | 239 | 88 | 90 | 102 | Minor response |
| 18 | 149 | 102 | 114 | 455 | 366 | 215 | 69 | 120 | 104 | Stable disease |
| 19 | 124 | 129 | 129 | 521 | 334 | 243 | 49 | 51 | 64 | Stable disease |
| 20 | 140 | 128 | 126 | 404 | 158 | 138 | 77 | 128 | 111 | Stable disease |
| 21 | 134 | 100 | 101 | 237 | 329 | 283 | 57 | 248 | 269 | Stable disease |
| 22 | 144 | 114 | 123 | 339 | 409 | 342 | 81 | 88 | 120 | Progressive disease |
| 23 | 146 | 123 | 118 | 231 | 162 | 157 | 65 | 73 | 71 | Stable disease |
| 24 | 137 | 103 | 118 | 218 | 225 | 186 | 78 | 101 | 97 | Progressive disease |
| 25 | 134 | 137 | 136 | 301 | 300 | 267 | 91 | 145 | 147 | Stable disease |
| 26 | 138 | 125 | 127 | 181 | 222 | 138 | 77 | 67 | 70 | Progressive disease |
| 27 | 134 | 114 | 105 | 544 | 378 | 303 | 49 | 79 | 49 | Stable disease |
| Mean ± SD | 131 ± 14 | 117 ± 13 | 114 ± 14 | 306 ± 123 | 263 ± 82 | 197 ± 70 | 66 ± 14 | 100 ± 44 | 97 ± 45 | |

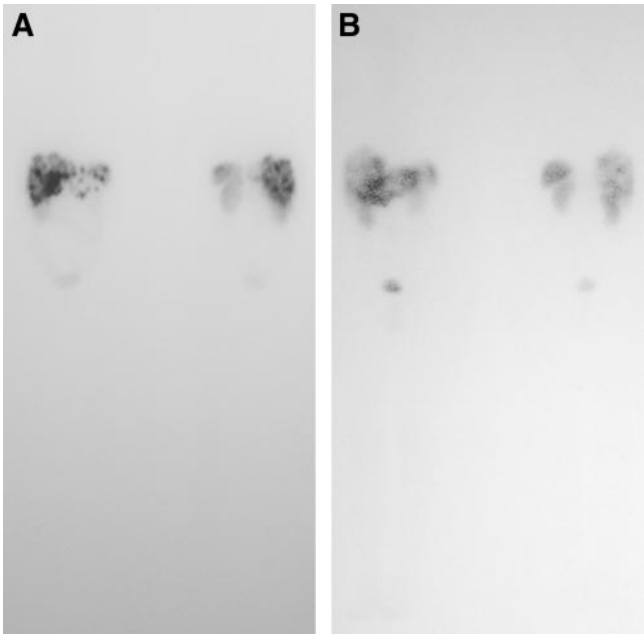


**FIGURE 1.** Anterior whole-body scans of patient 9. (A) Scan obtained 24 h after injection of 7,400 MBq of $^{177}$Lu-DOTATOC shows several abdominal metastases (liver, spleen, and lymph nodes). (B) Scan obtained 6 h after injection of 185 MBq $^{111}$In-Octreoscan 6 mo after treatment with 7,400 MBq of $^{177}$Lu-DOTATOC shows a decrease in tumor load. Especially, a reduction of liver metastases can be seen.

mo (mean, 8.3 ± 3.4 mo). Presently, 8 patients are still without disease progression; therefore, the overall time to progression will increase further.

## DISCUSSION

The labeling of $^{177}$Lu-DOTATOC was straightforward, and its application was safe. No serious adverse events occurred.

The group of 27 patients was selected from patients treated earlier with $^{90}$Y-DOTATOC; all showed stable disease, a minor response, or partial remission after treatment but experienced relapse rather early and a short time to progression (15 ± 7.8 mo) The time to progression after treatment with $^{90}$Y-DOTATOC in these patients was shorter than has been reported in the literature (*18*).

The absorbed doses to normal organs, especially to the kidneys, were low. In previous clinical trials, a cumulative absorbed dose to the kidneys of 23 or 27 Gy was taken as the maximum tolerated dose (*11,26,29*). But these values are controversial (*30*) because they are derived from external-beam radiation (*31*) with a potentially different mechanism. The low absorbed doses are compatible with the fact that no increase of creatinine levels was found.

When the clinical results after $^{177}$Lu-DOTATOC are correlated with the clinical results after $^{90}$Y-DOTATOC, a good response after $^{90}$Y-DOTATOC (partial remission in our patients) is obviously a positive prognostic factor for further radionuclide treatment. Some tumors seem to be especially suited for peptide receptor–mediated radionuclide therapy. Two reasons are possible: There could be a high density of somatostatin receptors leading to a high radiation-absorbed dose, or there could be some tumors that are more radiosensitive than others.

The general condition of the patients was not scaled before treatment with $^{177}$Lu-DOTATOC but was worse than before the first treatment with $^{90}$Y-DOTATOC because all patients had a longer history of illness and experienced progression after remission or stabilization after $^{90}$Y-DOTATOC therapy. The total amount of injected activity (fixed activity, 7,400 MBq of $^{177}$Lu-DOTATOC) was rather low because we included patients with an increased serum creatinine level or with a diminished hemoglobin level.

The toxicity in patients with increased creatinine or diminished hemoglobin levels was not different from that in patients with normal values. We found no severe toxicity and, especially, no increase of creatinine levels. Therefore, we conclude that the treatment with $^{177}$Lu-DOTATOC in cases of relapse after treatment with $^{90}$Y-DOTATOC is feasible and safe. Clinical improvement could be observed, and most patients benefited from the treatment.

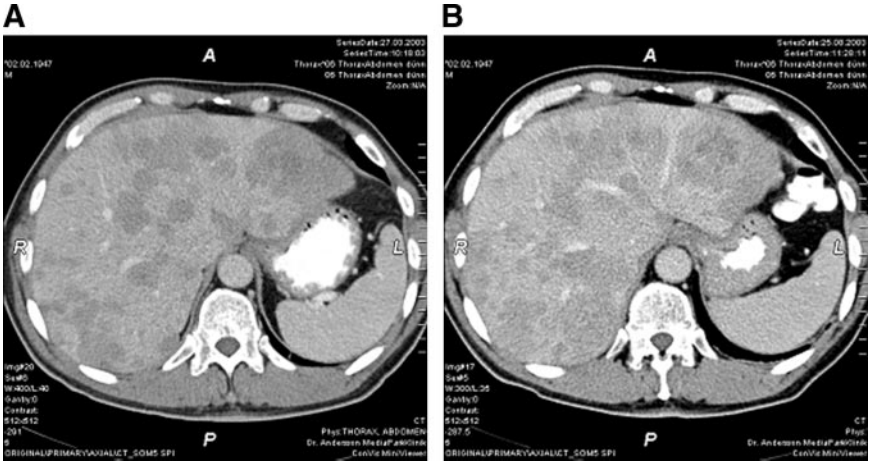


**FIGURE 2.** CT scans of patient 9. (A) Nine months after treatment with $^{90}$Y-DOTATOC and 4 wk before treatment with $^{177}$Lu-DOTATOC, CT scan shows multiple liver metastases. (B) Corresponding CT scan 4 mo after treatment with $^{177}$Lu-DOTATOC shows minor response.

With regard to the radiobiologic mechanisms of $^{177}$Lu and $^{90}$Y, the combination of the 2 radionuclides could improve the biologic efficiency. The high-energy β-emitter $^{90}$Y deposits high doses to tumors and also to areas with low target protein expression and to heterogeneous tumor tissue. Because of the strong crossfire effect, parts of the tumor that either are poorly differentiated and therefore have a low density of somatostatin receptors or are poorly vascularized can be reached. $^{177}$Lu, on the other hand, seems to have more favorable physical characteristics for the treatment of small tumors (*32–34*).

Another mechanism that is not well defined is the so-called low-dose hypersensitivity-inducible radioresistance hypothesis as described by Joiner et al. (*35*). The administration of only a low absorbed dose at a low dose rate might be more effective in inducing tumor cell death than are higher absorbed doses.

## CONCLUSION

Treatment with $^{177}$Lu-DOTATOC of patients who were pretreated with $^{90}$Y-DOTATOC is feasible and appears to be safe even when patients present with grade 1 or 2 hematotoxicity or nephrotoxicity. Clinical response at a low injected activity is promising. A good response after treatment with $^{90}$Y-DOTATOC is a positive predictor for successful treatment with $^{177}$Lu-DOTATOC.

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