Combination Radionuclide Therapy Using ^{177}Lu- and ^{90}Y-Labeled Somatostatin Analogs

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Peptide receptor-targeted radionuclide therapy of somatostatin receptor-expressing tumors is a promising application of radiolabeled somatostatin analogs. Suitable radionuclides are ^{90}Y, a pure, high-energy β-emitter (2.27 MeV), and ^{177}Lu, a medium-energy β-emitter (0.5 MeV) with a low-abundance γ. **Methods:** Lewis rats, each bearing both a small (approximately 0.5 cm^2) and a large (7–9 cm^2) somatostatin receptor-positive rat pancreatic CA20948 tumor in their flanks, were used. We investigated the radiotherapeutic effects of [^{90}Y-tetraazacyclododecanetetraacetic acid (DOTA),Tyr^3]octreotide, [^{90}Y-DOTA,Tyr^3]octreotate, [^{177}Lu-DOTA,Tyr^3]octreotate, and the combination of ^{90}Y- and ^{177}Lu-labeled analogs at the same tumor radiation dose (60 Gy). **Results:** Radiotherapeutic effects of the ^{90}Y- and ^{177}Lu-labeled analogs were found in the rat tumor model. In these animals bearing tumors of different sizes, the antitumor effects of the combination of 50% ^{177}Lu- plus 50% ^{90}Y-analogs were superior to those in animals treated with either ^{90}Y- or ^{177}Lu- analog alone. In smaller tumors, the ^{90}Y radiation energy was not completely absorbed in the tumor, whereas in larger tumors the increased number of clonogenic tumor cells at the fixed level of absorbed dose may account for the failure of ^{177}Lu alone to go completely into remission. **Conclusion:** This study shows the superior antitumor effects of the combination of ^{177}Lu- and ^{90}Y-somatostatin analogs when compared with either ^{90}Y- or ^{177}Lu-analog alone in animals bearing tumors of various sizes.

Key Words: ^{90}Y; ^{177}Lu; somatostatin analogs; tumor size; peptide-receptor radionuclide therapy

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Radiolabeled receptor-binding peptides have been shown to be an important class of radiopharmaceuticals for tumor diagnosis and therapy. The specific and high-affinity receptor-binding property of the peptide can be exploited by labeling with a radionuclide and using the radiolabeled peptide as a vehicle to guide radioactivity to tissues expressing a particular receptor. The high affinity of the peptide for its receptor and the internalization of the receptor–peptide complex facilitates retention of the radionuclide in receptor-expressing tumors, whereas its relatively small size facilitates rapid clearance from the blood. Peptides most successfully applied for these purposes are somatostatin analogs that bind to receptors overexpressed on neuroendocrine tumors (*1*). Peptides labeled with γ- or positron emitters enable noninvasive visualization of receptor-expressing tumors. In addition, when labeled with therapeutic radionuclides these peptides have the potential to eradicate receptor-expressing tumors—an approach referred to as peptide receptor radionuclide therapy (PRRT).

Currently, ^{90}Y, a pure, high-energy β-emitter (2.27 MeV), and ^{177}Lu, a medium-energy β-emitter (0.5 MeV) with a low-abundance γ, are the most frequently used radionuclides in PRRT. We have previously shown that the somatostatin analog [tetraazacyclododecanetetraacetic acid (DOTA),Tyr^3]octreotide (DOTATOC) (Fig. 1) can form a stable complex with ^{90}Y (*2,3*). In rats with subcutaneous tumors, ^{90}Y-DOTATOC effectively controlled tumor growth (*4*). Studies to determine the therapeutic efficacy of ^{90}Y-DOTATOC in patients with cancer are ongoing at various institutions (*5–14*). The most promising rate of complete plus partial responses seen in the various ^{90}Y-DOTATOC studies consistently exceeds that obtained with [^{111}In-diethylenetriaminepentaacetic acid]octreotide (*15*).

The new somatostatin analog Tyr^3-octreotate has an increased receptor affinity compared with octreotide and Tyr^3-octreotide (*16,17*). We investigated the antitumor effects of [^{177}Lu-DOTA,Tyr^3]octreotate (DOTATATE) (Fig. 1) in various models, including a rat liver micrometastatic tumor model and subcutaneous tumor models. ^{177}Lu-DOTATATE showed excellent antitumoral effects in both tumor models (*18,19*).

When patients with gastroenteropancreatic neuroendocrine tumors were treated with ^{177}Lu-DOTATATE, complete or partial remissions were documented in an impressive 30% of patients and minor responses in 21%, whereas 26% of patients with progressive disease at the start of PRRT showed stabilization (*20*).

Comparison of the characteristics of the β-emitters ^{177}Lu and ^{90}Y (Table 1) shows that each has specific potential advantages for tumor therapy. ^{90}Y particles have higher energies and longer particle ranges, leading to more radio-
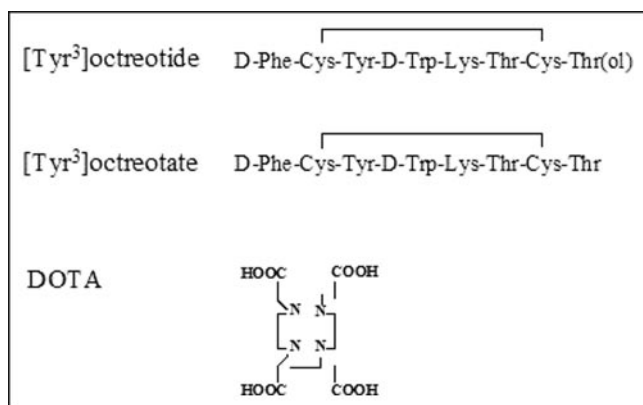
FIGURE 1. Structures of the somatostatin analogs Tyr³-octreotide and Tyr³-octreotate and of the chelator DOTA.

activity in the tumor cell per peptide molecule and to a better crossfire through the tumor, which is especially advantageous in larger tumors and in tumors with heterogeneous receptor distribution. The shorter half-life of ^{90}Y leads to a higher dose rate. ^{177}Lu particles, on the other hand, have lower energy and smaller particle range, leading to better absorption in smaller tumors (Table 2). In addition, ^{177}Lu emits γ-radiation with an energy suitable for scintigraphy, enabling dosimetry during PRRT, and also has a longer half-life, making shipping more convenient.

In preclinical PRRT studies, good tumor responses were found using either ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC. Effects, however, varied with tumor size, consistent with a computer model of tumor cure that calculated that ^{177}Lu should work optimally in small tumors, whereas ^{90}Y would be better for larger tumors (4,19,21).

The aim of the current studies was to expand on previous studies in rats using the clinically applied somatostatin analogs for PRRT, ^{177}Lu-DOTATATE, ^{90}Y-DOTATOC, or their combination, in rats bearing 2 tumors of different sizes. To exclude the effects of different peptide analogs used in the clinical studies (i.e., octreotate and octreotide), we also studied the PRRT effects of the same peptide analog, DOTATATE, labeled with ^{90}Y or ^{177}Lu.

The combination of different therapy modalities holds interest as a means of improving the clinical therapeutic effects of radiolabeled peptides. This includes the potential of a combination of different radionuclides, such as ^{177}Lu-

TABLE 1
Characteristics of ^{90}Y, ^{177}Lu, and ^{131}I

Isotope	Maximum energy (keV)	Maximum range (mm)	Half-life (d)
^{90}Y	2,270	12.0	2.7
^{177}Lu	497	2.1	6.7
^{131}I	606	2.4	8

TABLE 2
Percentage Energy Absorption of ^{90}Y and ^{177}Lu β-Emissions in Spheres (23)

Sphere diameter (mm)	Energy absorption (%)	
	^{90}Y	^{177}Lu
50	95	100
30	91	99.6
10	66	97
5	41	93
3	26	88
1	9	67
0.1	1	15

and ^{90}Y-labeled somatostatin analogs, to reach a wider tumor region.

MATERIALS AND METHODS

Radiolabeled Peptides

^{90}YCl$_3$ (NEN Life Science Products Inc.), ^{177}Lu (IDB Holland BV), and DOTATATE (BioSynthema) were obtained from commercial sources. DOTATOC was synthesized as described in a previous publication (22). ^{90}Y labeling of DOTATOC/DOTATATE and ^{177}Lu labeling of DOTATATE also were performed as described previously (3,19).

Animals

Rat CA20948 pancreatic tumors were grown in the flanks of male Lewis rats (weight, 250–300 g). Five hundred microliters of a cell suspension of CA20948 tumor, prepared from 5 g of crude, viable tumor tissue in 100 mL saline, were injected subcutaneously into one flank, with an injection into the other flank about 3 weeks later. After 7–27 d, rats bearing 2 tumors of different sizes were anesthetized and ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, or a combination of ^{90}Y- and ^{177}Lu-labeled analogs at the same tumor radiation dose was injected into the dorsal vein of the penis. The specific activities of ^{90}Y-DOTATOC/DOTATATE and ^{177}Lu-DOTATATE were 37 MBq/1.2 μg peptide and 37 MBq/μg peptide, respectively. Groups of 8–15, with an average of 12 rats per group, were studied. Control groups did not receive radiolabeled octreotide.

Tumor growth (determined by measurement of the 2 largest perpendicular diameters using a caliper ruler), animal condition, and body weight were assessed at regular intervals. In addition to 10% loss of original body weight, tumor growth beyond approximately 15 cm^2 was used as a progression point at which animals were sacrificed.

Statistical analysis was performed on survival curves using the logrank test (GraphPad Prism 4).

Dosimetry

The dose to rat tumors in grays was calculated assuming uniform distribution of radioactivity in a spheric mass. Only tumor-to-tumor dose was considered, and S values (mean absorbed dose per unit cumulated activity) for ^{177}Lu and ^{90}Y in spheres of appropriate size were used with tumor uptake data from biodistribution studies as described previously (4,19,23).

RESULTS

PRRT Using ^{177}Lu-DOTATATE, ^{190}Y-DOTATOC, and a Combination

Tumors of rats in the control group and in the group treated with 370 MBq ^{90}Y-DOTA grew excessively, with no survival beyond 150 d (Fig. 2A). Administration of any unlabeled peptide in the same amounts used during PRRT also resulted in no tumor response (data not shown). After injection of 370 MBq ^{90}Y-DOTATOC or 555 MBq ^{177}Lu-DOTATATE, each leading to doses of 60 Gy to the larger tumors, survivals were somewhat better, although in these groups few rats survived the full period of 150 d (the rat equivalent of human 5-y survival). Significantly better ($P <$ 0.001) survival was seen after PRRT with the combination of 185 MBq ^{90}Y-DOTATOC and 278 MBq ^{177}Lu-DOTATATE (Fig. 2A). Areas under the curve were 34, 42, 75, 75, and 130 d for control rats and rats treated with ^{90}Y-DOTA, ^{90}Y-DOTATOC, ^{177}Lu-DOTATATE, and the combination, respectively.

For the combination of ^{177}Lu- and ^{90}Y-labeled analogs, the median survival (the time point at which 50% of the rats died) was not reached by 150 d, whereas for the other groups this point was at 75 d or less, showing the superior effects of the combination therapy.

Figure 2B illustrates the criteria used for euthanasia in the various rat groups. These included tumor growth beyond the maximum size of 15 cm^2 for tumors classified as large at start of therapy, for tumors classified as small at the start of therapy, or for both tumors. When no tumors grew after therapy, animals were sacrificed at day 150 after therapy. Control animals and animals treated with ^{90}Y-DOTA were sacrificed because the large tumor reached 15 cm^2 first, although at the same time all small tumors were growing quickly. Only after PRRT with ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC was there sufficient tumor growth inhibition in the large tumor in some animals to allow the small tumor to

equal its size. In these animals, the criterion for euthanasia was that both tumors reached 15 cm^2. The percentage of such animals was higher after ^{90}Y-DOTATOC than after ^{177}Lu-DOTATATE PRRT, showing the greater capacity of ^{90}Y to control growth in larger tumors. Combination therapy, however, achieved by far the best response, with 60% of animals surviving 150 d after PRRT.

PRRT Using ^{177}Lu-DOTATATE, ^{90}Y-DOTATOC, and a Combination

Tumors of rats in the control group grew rapidly. After injection of 2 × 111 MBq ^{90}Y-DOTATATE (2 injections, 2 weeks apart) or 2 × 278 MBq ^{177}Lu-DOTATATE (2 injections, 2 weeks apart) leading to doses of 60 Gy to the larger tumors, survivals were somewhat better than in the first study. Twenty-five percent of the animals survived the 150 d (Fig. 3A). Significantly better ($P < 0.001$) survival was observed after PRRT with the combination of 2 × 56 MBq ^{90}Y-DOTATOC and 2 × 140 MBq ^{177}Lu-DOTATATE. Areas under the curve were 18, 88, 96, and 125 d for control rats and rats treated with ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, and the combination, respectively.

For the combination of ^{177}Lu- and ^{90}Y-labeled analogs, median survival was not reached by 150 d, whereas for the other groups it was ≤95 d, showing the superior effects of the combination therapy.

Figure 3B illustrates the criteria used for killing in the various rat groups. Again, control animals were killed when the "large" tumor reached 15 cm^2 first. Only after PRRT with ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC was there sufficient tumor growth inhibition of the large tumor in these animals to allow the small tumor to equal at least the large tumor in size. By far the best response was reached after combination therapy, with 62% of the animals surviving 150 d after PRRT.
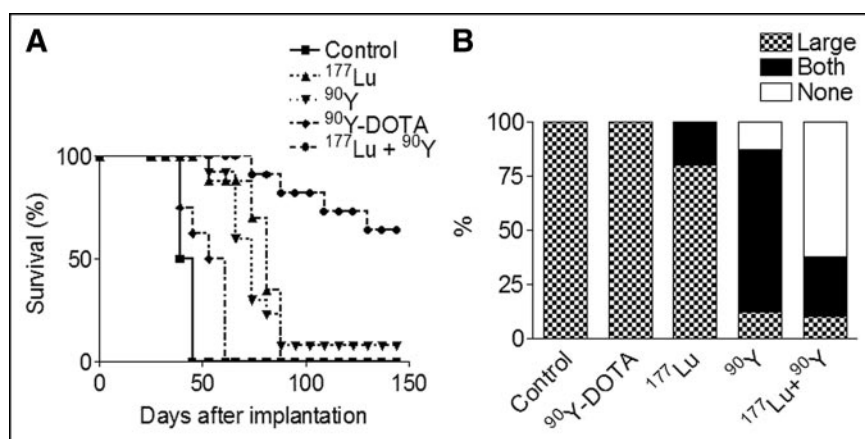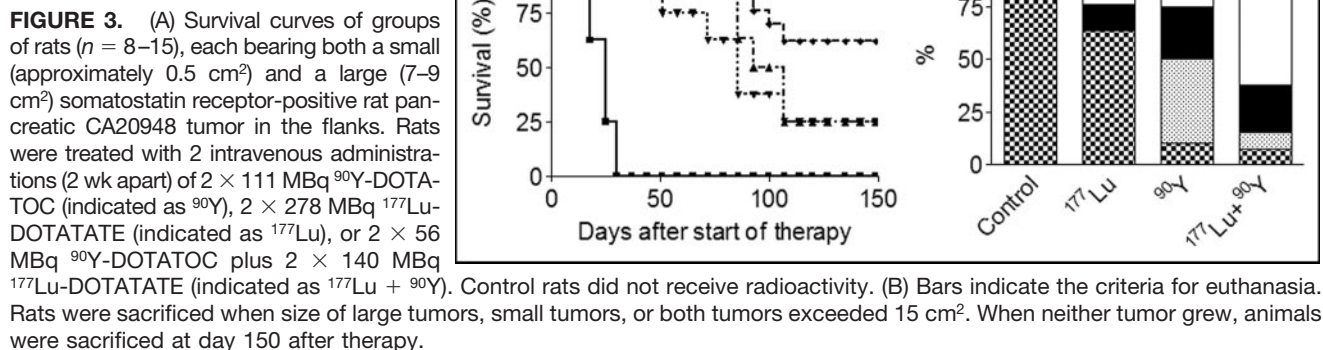

FIGURE 2. (A) Survival curves of groups of rats (n = 8–15), each bearing both a small (approximately 0.5 cm^2) and a large (7–9 cm^2) somatostatin receptor-positive rat pancreatic CA20948 tumor in the flanks. Rats were treated with single intravenous administrations of 370 MBq ^{90}Y-DOTATOC (indicated as ^{90}Y), 370 MBq ^{90}Y-DOTA, 555 MBq ^{177}Lu-DOTATATE (indicated as ^{177}Lu), or 185 MBq ^{90}Y-DOTATOC plus 278 MBq ^{177}Lu-DOTATATE (indicated as ^{177}Lu + ^{90}Y). Control rats did not receive radioactivity. (B) Bars indicate the criteria for euthanasia. Rats were sacrificed when size of large tumors, small tumors, or both tumors exceeded 15 cm^2. When neither tumor grew, animals were sacrificed at day 150 after therapy.

FIGURE 3. (A) Survival curves of groups of rats (n = 8–15), each bearing both a small (approximately 0.5 cm²) and a large (7–9 cm²) somatostatin receptor-positive rat pancreatic CA20948 tumor in the flanks. Rats were treated with 2 intravenous administrations (2 wk apart) of 2 × 111 MBq ^{90}Y-DOTA-TOC (indicated as ^{90}Y), 2 × 278 MBq ^{177}Lu-DOTATATE (indicated as ^{177}Lu), or 2 × 56 MBq ^{90}Y-DOTATOC plus 2 × 140 MBq ^{177}Lu-DOTATATE (indicated as ^{177}Lu + ^{90}Y). Control rats did not receive radioactivity. (B) Bars indicate the criteria for euthanasia. Rats were sacrificed when size of large tumors, small tumors, or both tumors exceeded 15 cm². When neither tumor grew, animals were sacrificed at day 150 after therapy.

These data show again the promise of PRRT using ^{177}Lu and ^{90}Y and the potential of the combination of these radionuclides with different β-energies and particle ranges to achieve higher cure rates in tumors of various size.

DISCUSSION

PRRT using radiolabeled somatostatin analogs is a promising new treatment option for patients with metastasized, somatostatin receptor-positive neuroendocrine tumors. One advantage of PRRT is that radiation can be delivered selectively not only to (large) primary tumors but also to subclinical tumors and metastases that are too small to be imaged and thereby identified for surgery or external beam radiotherapy. Clinical trials have demonstrated that both ^{177}Lu and ^{90}Y are suitable β-emitting radionuclides for PRRT. ^{177}Lu and ^{90}Y differ markedly in their physical properties, including half-life, path length, and type of energy emissions (Table 1). Potential advantages of ^{177}Lu for PRRT include a longer half-life, an emission spectrum that allows for dosimetric studies and therapy using the same compound, and β-particle ranges suitable for small tumors (Table 2). By contrast, ^{90}Y emits β-particles with longer path lengths and higher energies and so may be preferable to ^{177}Lu for patients with bulky disease, poorly vascularized solid tumors, or tumors with heterogeneous receptor distribution. However, given the high tumor-absorbed doses for patients receiving PRRT and the relatively long particle range of ^{90}Y β-emissions used for PRRT, there is a possibility of large absorbed doses to tissues adjacent to or surrounding small tumors. Because tumors may be adjacent to critical organs, normal tissues may receive large absorbed doses.

Sparks et al. (24) studied the deposition of energy from emissions of ^{131}I (with characteristics similar to ^{177}Lu) and ^{90}Y to assess the possible magnitude of absorbed doses in tissues adjacent to tumors. Mathematic models were con-structed to simulate situations such as tumor wrapped around a small cylinder (e.g., a nerve or artery), tumor against a tissue (e.g., the pericardium or wall of any gastrointestinal tract organ), and tumor surrounded by any soft tissue. The absorbed dose for tissues close to tumors containing ^{90}Y ranged from 24% of tumor absorbed dose at 1 mm from the tumor to 103% of tumor absorbed dose for small structures (such as nerves or arteries) surrounded by tumor. For tissues close to tumors containing ^{131}I, this range was 4%–46%. This study showed that when absorbed doses to tumors are high, absorbed dose to adjacent tissues can also be high, potentially causing toxicities. Doses to adjacent tissues vary with tumor size and the energy of the radionuclide. ^{90}Y seems less suitable for PRRT of small tumors, because very small tumors will not be able to absorb all electron energy emitted by ^{90}Y in the tumor cells (4) (Table 2).

^{177}Lu β-emissions, on the other hand, have energies and particle ranges much more suitable for treatment of small tumors. However, with the increase of clonogenic cells in larger tumors, the probability of cure decreased more rapidly than with ^{90}Y. This might be explained by a lack of uniformity of the activity distribution over the tumor, because for nonuniform activity distributions, even at the same average dose, a higher energy emitter will produce a more uniform and therefore more effective absorbed dose distribution. Another relevant factor in the comparison of ^{177}Lu and ^{90}Y is the difference in half-life. Because ^{177}Lu has a longer half-life, it will take longer to deliver the same dose as ^{90}Y (i.e., the dose rate will be lower). This will render it less effective, because the tumor cell population will have more time for proliferative regeneration.

To treat patients with tumors of various sizes with non-homogenous receptor distribution, a possible solution might therefore be the use of a combination of radionuclides (e.g.,

the high-energy ^{90}Y for large tumors and a low-energy β-emitter, such as ^{177}Lu, for smaller tumors and metastases).

These results showed striking radiotherapeutic effects achieved by the combination of ^{177}Lu- and ^{90}Y-labeled somatostatin analogs in tumors of different size, in agreement with a mathematical model evaluating tumor curability using 22 different β-emitting radionuclides in relation to tumor size (*21*). The model yielded an optimal tumor size for curability for the different radionuclides. The optimal tumor diameter calculated for ^{90}Y was 34 mm, in the same range as the larger tumor diameters in the studies, and the optimal tumor diameter calculated for ^{177}Lu was 2 mm, in the same range as the smaller tumor diameters in our studies.

Although this report focuses on the effects of combination therapy using simultaneous administration of ^{177}Lu- and ^{90}Y-somatostatin analogs, another interesting option is repeated administration with these analogs (e.g., an initial administration of ^{90}Y-labeled analog to treat the larger tumors, followed by ^{177}Lu-labeled analog in the next treatment cycle(s) for treatment of smaller metastases).

CONCLUSION

These studies show the potential of the combination of radionuclides with different β-energies and particle ranges to achieve higher cure rates in tumors of various sizes.

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