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The Inhibitory Effect of ^{111}In-DTPA^0-Octreotide on Intrahepatic Tumor Growth After Partial Hepatectomy

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The aim of this animal study was to evaluate whether peptide receptor radionuclide therapy with ^{111}In-diethylenetriaminepentaacetic acid (DTPA)^0-octreotide was able to reduce tumor growth even under tumor growth–stimulating conditions induced by partial hepatectomy (PHx). **Methods:** Rats underwent 70% PHx or sham operation. The development of hepatic metastases was determined 21 d after direct injection of somatostatin receptor (SS-R)–positive or SS-R–negative tumor cells into the portal vein. Groups of 8 or 9 animals that underwent PHx or sham operation were treated with octreotide 50 μg/kg subcutaneously twice daily or with 370 MBq ^{111}In-DTPA^0-octreotide intravenously on days 1 and 8. Both treatments were compared with control treatment. Forty non–tumor-bearing rats were used to determine the influence of ^{111}In-DTPA^0-octreotide therapy on liver regeneration after PHx. **Results:** PHx induced an increase in tumor growth in all experiments ($P < 0.01$). Octreotide treatment did not influence tumor growth after PHx or sham operation. ^{111}In-DTPA^0-octreotide could effectively reduce tumor growth in the liver of SS-R–positive tumors also under conditions of increased tumor growth as generated by PHx ($P < 0.01$). ^{111}In-DTPA^0-octreotide was also effective on SS-R–negative tumors after PHx ($P = 0.01$) but not after sham operation. Furthermore, ^{111}In-DTPA^0-octreotide therapy did not influence liver regeneration or liver function after PHx. **Conclusion:** Peptide receptor radionuclide therapy with ^{111}In-DTPA^0-octreotide is effective in SS-R–positive tumors. During liver regeneration, the growth of SS-R–negative tumors is also reduced. This effect is not induced by impairment of liver regeneration or liver function. Radionuclide therapy could therefore be a promising treatment modality for patients with symptomatic liver metastases of neuroendocrine tumors in combination with liver resection.

Key Words: peptide receptor radionuclide therapy; ^{111}In-DTPA^0-octreotide; liver metastases; partial hepatectomy

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Somatostatin (SS) is a small regulatory peptide, produced by degradation of a precursor protein, which inhibits the release of various hormones and may act as a neurotransmitter in the central nervous system (*1*). Several experimental and clinical studies also suggest that SS and its analogs have an antiproliferative effect (*2–5*). Critical to these actions is the presence of an SS receptor (SS-R), which, like other membrane receptors, subserves 2 functions: to recognize the ligand and bind it with high affinity and specificity, and to generate a transmembrane signal that evokes a biologic response. At least 5 different human SS-R subtypes have been cloned; however, most human SS-R–positive tumors express the second of these subtypes (*6*). For the visualization of SS-R–positive tumors in vivo, SS-R scintigraphy with ^{111}In-diethylenetriaminepentaacetic acid (DTPA)^0-octreotide (OctreoScan; Mallinckrodt Inc., Hazelwood, MO) is used, and this technique has become an important diagnostic tool in the management of patients with SS-R–positive tumors (*6,7*). ^{111}In emits not only γ-rays, which can be visualized with a gamma camera, but also internal conversion electrons and Auger electrons with a medium to short tissue penetration (200–550 μm to 0.02–10 μm) (*6,8*). In vivo, ^{111}In-DTPA^0-octreotide binds to the SS-R, and the ligand, including ^{111}In, is internalized and transported into the lysosomes. ^{111}In has a long residence time in the tumor cells (biologic half-life > 700 h) (*6,9*). This internalization by tumor cells of the radioligand in vivo is an important aspect for peptide receptor radionuclide therapy (PRRT). We previously reported the antiproliferative effect of PRRT with ^{111}In-DTPA^0-octreotide on the growth of SS-R–positive CA-20948 pancreatic tumor cells in the liver. We demonstrated that this effect of PRRT is SS-R–dependent by showing that blocking the receptors with a high dose of nonradioactive octreotide stopped this growth inhibitory effect almost completely. Moreover, no effect was achieved with SS-R–negative CC531 colon carcinoma cells (*10*).

Resections of hepatic metastases of gastroenteropancreatic tumors, which are predominantly SS-R–positive, are mostly performed with palliative intent because, in most cases, a diffuse pattern of metastases is present at laparotomy. As we demonstrated earlier, partial hepatectomy (PHx) dramatically stimulates tumor growth within the regenerating liver (*11*), probably because of tumor growth–promoting factors released after hepatectomy, such as hepatic growth factor, insulin growth factor I, and several cytokines. Therefore, we wanted to see whether the effect of PRRT on the growth of intrahepatic tumors in a model with accelerated intrahepatic tumor growth was also effective. In addition, we studied whether this effect of PRRT on tumor proliferation after PHx could probably be due to inhibition of liver regeneration. The putative tumor growth–inhibiting effect of PRRT after PHx could have implications for further clinical trials in patients with SS-R–positive tumors and liver metastases.

MATERIALS AND METHODS

Animals

Male rats of the inbred Wistar Albino Glaxo (WAG) and Lewis strain, which were 10–14 wk old and 225–250 g (Harlan-CPB, Austerlitz, The Netherlands), were kept under standard laboratory conditions (12 h light/12 h dark) and were given a standard laboratory diet (Hope Farms, Woerden, The Netherlands) and water ad libitum (*10*). The experimental protocol adhered to the rules laid down by the Dutch Animal Experimentation Act and was approved by the Committee on Animal Research of the Erasmus Medical Centre Rotterdam.

Tumors

The pancreatic tumor, CA-20948, was originally induced by azaserine (*12*). The SS-R–positive tumor is of acinar origin and is transplantable in syngeneic Lewis rats. The tumor was transplanted and maintained in the liver by direct injection into the portal vein. To produce artificial liver metastases, tumors were excised from donor livers, cleaned from normal liver tissue, and pressed through sieves with decreasing mesh size. The resulting suspension was washed twice in Roswell Park Memorial Institute (RPMI) 1640 medium (Gibco, Paisly, U.K.). Viability was measured with trypan-blue exclusion (0.3% in a 0.9% NaCl solution). A suspension of 2.5×10^6 living cells per milliliter was used for direct injection into the portal vein.

Tumor CC531 is an SS-R–negative, 1,2-dimethylhydrazine–induced, moderately differentiated colon adenocarcinoma transplantable in syngeneic WAG rats (*13*). The tumor is maintained in tissue culture as a monolayer in RPMI 1640 medium supplemented with 5% fetal calf serum. The cells were harvested from stationary cultures by gentle treatment with trypsin. A suspension of 2.5×10^6 living cells per milliliter was used for direct injection into the portal vein. The presence or absence of the SS-R on both tumor cell lines was determined by specific binding of ^{125}I-Tyr^3-octreotide. This binding was found to membrane preparations of CA-20948 pancreatic tumor cells (inhibitory concentration of 50%, 0.6 nmol/L; maximum number of binding sites, 110 fmol/mg membrane protein), whereas no binding was found to membrane preparations of the CC531 colon tumor cells (*5*).

Radiolabeling and Quality Control of Radioligand

DTPA^0-octreotide (pentetreotide, DRN 4920) and $^{111}InCl_3$ (DRN 4901, 370 MBq/mL in HCl, pH 1.5–1.9) were obtained from Mallinckrodt Medical (Petten, The Netherlands). Octreotide was a gift of Novartis, Preclinical Research (Basle, Switzerland). The labeling was performed by diluting the freeze-dried DTPA^0-octreotide in 1 mL saline and adding this to the $^{111}InCl_3$. Thirty minutes after the start of this procedure, quality control was performed by instant thin-layer chromatography with silica gel and 0.1 mol/L sodium citrate, pH 5, as eluent, as described earlier (*10*). The labeling efficiency of ^{111}In-DTPA^0-octreotide was more than 98%. Each administration of the radioligand into the dorsal penis vein consisted of 370 MBq ^{111}In labeled with 0.5 μg DTPA^0-octreotide, referred to as 370 MBq ^{111}In-DTPA^0-octreotide.

Experimental Procedure in Tumor-Bearing Rats

With the rats under ether anesthesia, the abdomen was opened through a midline incision. The left lateral and median liver lobes, representing 70% of the liver volume, were freed of fibrous attachments. The circulation in these lobes was temporarily interrupted by ligation of the hilar vessels. Then, 0.5×10^6 viable, SS-R–positive CA-20948 cells, suspended in 0.2 mL RPMI 1640 medium, were injected slowly into the portal vein through a 0.4×12 mm needle. During 2 min, the tumor cells were directed through the remaining 30% of the liver that was not ligated. The rats were then randomized into a 70% PHx group and a nonhepatectomy group (sham). In the PHx group, the temporary ligation was replaced by a permanent 2-0 silk tie and the ligated lobes were resected. In the sham group, the temporary ligation was removed 2 min after the injection to reestablish the circulation. At the end of both procedures, the liver was returned to the peritoneal cavity and the laparotomy wound was closed in 1 layer. On day 1 after the operation, rats from both the PHx group and the sham group were randomized into experimental and control groups. All rats were sacrificed 21 d after inoculation of tumor cells. The livers were removed, immersed in phosphate-buffered saline, dried, and weighed. Tumor growth was determined by 2 investigators who, while unaware of the treatment modality, counted the number of metastases on the surface of the liver lobes and determined the affected percentage of the liver in rats with more than 100 tumor colonies. In the parallel experiment, the same procedure was performed when 0.5×10^6 viable, SS-R–negative CC531 cells were injected. Experimental groups contained 8 or 9 animals.

Treatment with Octreotide

Sixteen rats were injected with SS-R–positive CA-20948 tumor cells into the portal vein. Eight rats were treated with octreotide (Sandostatin; Sandoz Pharmaceuticals, East Hanover, NJ), 50 μg/kg in 0.2 mL RPMI 1640 medium, subcutaneously in the neck. Treatment was given twice daily starting on the first day after the operation. Control treatment consisted of 0.2-mL injections of RPMI 1640 medium according to the same schedule.

Treatment with ^{111}In-DTPA^0-Octreotide

Sixteen rats were injected with SS-R–positive CA-20948 tumor cells into the portal vein and, in a parallel experiment, 16 rats were injected with SS-R–negative CC531 tumor cells. Rats in the experimental groups were treated with 370 MBq ^{111}In-DTPA^0-octreotide into the tail vein on days 1 and 8. Rats in the control groups were injected with vehicle, 0.5 μg DTPA^0-octreotide.

Effects of ^{111}In-DTPA^0-Octreotide on Liver Regeneration

Forty non–tumor-bearing WAG rats underwent PHx according to the procedure described above and were randomized into PRRT and control groups. Animals in the PRRT group received an intravenous injection of 370 MBq ^{111}In-DTPA^0-octreotide 24 h after PHx. Rats in the control group received an intravenous injection of 0.5 μg DTPA^0-octreotide. Four rats from each group were sacrificed at 2, 4, 8, 16, and 32 d after PHx. Functional recovery of the liver was determined with bromsulphalein (BSP) ($C_{20}H_8Br_4Na_2O_{10}S_2$) clearance during 45 min (*14*). One hour before sacrifice, 8 mg BSP per 100 g body weight were injected into the dorsal penis vein. Blood samples were drawn from the tail at 1 and 45 min after the injection of BSP. BSP concentrations in these samples were determined by colorimetry at a 586-nm wavelength. Clearance of BSP in 45 min is expressed as (1 − [BSP level after 45 min/BSP level after 1 min]) × 100.

Liver function analysis was performed by determining the serum levels of alanine transaminase, aspartate transaminase, γ-glutamyl transferase, alkaline phosphatase, bilirubin, protein, and albumin. All livers were weighed, and DNA synthesis was measured by the 5-bromo-5-iododeoxyuridine (BrdU) labeling index. In short, 90 min before sacrifice, 50 mg BrdU per kilogram of body weight were administered intraperitoneally. Samples of the remnant liver were fixed and embedded in paraffin. The labeling index of BrdU was expressed as the rate of 100-hepatocyte nuclear positivity in 5 fields at high-power magnification (×400).

Statistical Analysis

Statistical analysis was performed using the Mann–Whitney *U* test on categorized outcomes. Statistical significance was defined as $P < 0.05$.

RESULTS

Effects of Treatment with Octreotide

The results of octreotide treatment on the growth of SS-R–positive CA-20948 tumors in the liver are given in Table 1. In sham-operated animals, there was no difference in tumor growth between octreotide-treated animals and control animals 21 d after tumor cell injection. As found in earlier experiments, PHx resulted in a significant increase in tumor growth, compared with tumor growth after a sham operation, in both octreotide-treated animals and control animals ($P < 0.01$) (*11*). Octreotide treatment in rats that underwent PHx did not decrease tumor growth.

Effects of PRRT with ^{111}In-DTPA^0-Octreotide

The results of PRRT with 370 MBq ^{111}In-DTPA^0-octreotide on the growth of SS-R–positive CA-20948 tumors in the liver are summarized in Table 2. PRRT on days 1 and 8 induced a significant decrease in tumor growth in sham-operated animals ($P < 0.01$). Tumor growth was again greater after PHx than after sham operation ($P < 0.01$). Under these conditions of increased tumor growth, PRRT also decreased tumor growth ($P < 0.01$).

In the parallel experiment with SS-R–negative CC531 tumor cells (Table 3), PHx again increased tumor growth in both PRRT and control groups ($P < 0.01$). PRRT did not induce a difference in tumor growth in sham-operated animals. However, there was a significant decrease in tumor growth by PRRT after PHx also for these SS-R–negative tumors ($P = 0.01$). In this experiment, 1 rat died by an overdose of ether.

Effects of PRRT on Liver Regeneration

The influence of PRRT on liver regeneration after PHx was investigated in non–tumor-bearing animals. During the first 4 d, there was a rapid increase in liver weight, after which liver weight was almost completely restored. No difference in wet liver weight was found after 2, 4, 8, 16, or 32 d between rats that underwent PHx with or without PRRT (Fig. 1). There was also no difference in BrdU labeling index between these 2 groups at days 2 and 4 after PHx (Fig. 2). At later intervals in both groups, labeled hepatocytes were identified only sporadically, again without significant difference. Basic liver function tests after PHx showed no alteration by PRRT. In addition, BSP clearance was not influenced by PRRT (Fig. 3).

TABLE 1
Effect of Octreotide* on SS-R–Positive CA-20948 Liver Metastases After Sham Operation or 70% Partial Hepatectomy

Treatment	Mean liver weight (g)	Tumor score					
		0	1–20	21–50	51–100	>100†	>100‡
Sham operation							
Control ($n = 8$)	10.4 (0.9)	—	1	3	3	1	—
Octreotide ($n = 8$)	10.3 (1.0)	—	1	4	3	—	—
70% PHx							
Control ($n = 8$)§	16.1 (4.3)	—	—	—	—	2	6
Octreotide ($n = 8$)§	14.8 (2.6)	—	—	—	1	1	6

*50 μg/kg subcutaneously, twice daily.
†<50% of liver affected.
‡>50% of liver affected.
§$P < 0.01$ vs. sham operation.
Values in parentheses are SEM.

TABLE 2
Effect of PRRT with 370 MBq ^{111}In-DTPA^0-Octreotide on SS-R–Positive CA-20948 Liver Metastases After Sham Operation or 70% Partial Hepatectomy

Treatment	Mean liver weight (g)	Tumor score					
		0	1–20	21–50	51–100	>100*	>100†
Sham operation							
Control (n = 8)	17.3 (3.1)	—	1	—	—	2	5
PRRT (n = 8)	10.4 (0.4)	1	7	—	—	—	—
70% PHx							
Control (n = 8)‡	23.0 (2.7)	—	—	—	—	—	8
PRRT (n = 8)§	9.3 (1.1)	—	7	1	—	—	—

*<50% of liver affected.
†>50% of liver affected.
‡$P < 0.01$ vs. sham operation.
§$P < 0.01$ vs. controls.
Values in parentheses are SEM.

DISCUSSION

Surgical excision of liver tumors represents the only curative treatment for primary and metastatic liver malignancies. For colorectal tumors, the results of surgical resection compare favorably with the natural outcome for these selected groups of patients (*15*). However, despite the curative potential of hepatic resection, recurrence has been reported in 65%–80% of the patients. The predominant site of recurrence is within the remnant liver, and most recurrences are diagnosed within the first year after the operation (*16*,*17*). The high number of early recurrences suggests that resection might act as a double-edged sword. On one hand, survival after PHx is increased, but on the other hand, resection might provoke enhanced tumor growth. Clinical support for increased tumor growth after PHx was published recently. Elias et al. (*18*) demonstrated that during liver regeneration after right portal embolization, the growth rate of metastases in the left liver lobes is increased and even more rapid than the growth of liver parenchyma. These findings agree with a study on rats that demonstrated accelerated tumor growth in regenerating liver lobes and inhibited tumor growth in atrophied liver segments after selective portal embolization (*19*).

Several groups have found experimental evidence for stimulation of tumor growth by PHx in various animal models; both intrahepatic and extrahepatic tumors were found to grow more rapidly after PHx (*20*,*21*). We reported earlier, using the same model as in the present study, that the growth of SS-R–negative CC531 colon tumors was significantly greater in the remnant livers of rats that had undergone 70% liver resection than in the livers of sham-operated animals (*11*). We then reported that tumor necrosis factor α (TNF-α), administered intravenously, reduced this tumor growth–stimulating effect of PHx. TNF-α could be of benefit after PHx because TNF-α is known to stimulate rather than impair liver regeneration (*22*,*23*). However, clin-

TABLE 3
Effect of PRRT with 370 MBq ^{111}In-DTPA^0-Octreotide on SS-R–Negative CC-531 Liver Metastases After Sham Operation or 70% Partial Hepatectomy

Treatment	Mean liver weight (g)	Tumor score					
		0	1–20	21–50	51–100	>100*	>100†
Sham operation							
Control (n = 9)	14.1 (5.3)	1	2	5	1	—	—
PRRT (n = 9)	18.5 (8.0)	1	1	5	2	—	—
70% PHx							
Control (n = 9)‡	43.4 (8.0)	—	—	—	—	2	7
PRRT (n = 8)§	30.8 (5.6)	—	—	—	6	2	—

*<50% of liver affected.
†>50% of liver affected.
‡$P < 0.01$ vs. sham operation.
§$P < 0.01$ vs. controls.
Values in parentheses are SEM.

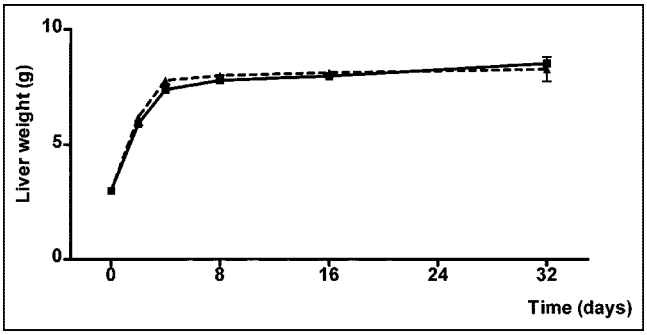

FIGURE 1. PRRT with ^{111}In-DTPA^{0}-octreotide and liver regeneration after 70% PHx. ▲ = control; ■ = PRRT.

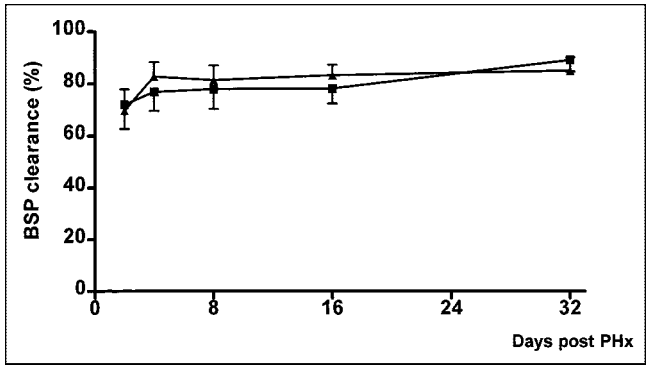

FIGURE 3. PRRT with ^{111}In-DTPA^{0}-octreotide and liver function after 70% PHx. ▲ = control; ■ = PRRT

ical use of TNF-α is limited to isolated perfusion because of severe toxicity after systemic administration (*24,25*).

If tumor growth is stimulated after PHx, the number of replicating tumor cells will be increased. Theoretically, this phase of tumor growth stimulation could be favorable for adjuvant chemotherapy, applied as adjuvant treatment, because the rapidly dividing tumor cells might be more susceptible to cytostatic agents. However, adjuvant treatment aiming at reduction of tumor growth stimulation caused by PHx might also impair liver regeneration and must therefore be applied clinically with great care, for it is the regenerating capacity of the liver that enables patients to recover from large resections (*26,27*). Several reports on studies of adjuvant chemotherapy, including doxorubicin and 5-fluorouracil, describe notable adverse effects caused by impairment of liver regeneration (*28*). An effective adjuvant treatment that does not impair regeneration could therefore be of value for patients with hepatic metastases.

For neuroendocrine liver metastases, which are mostly SS-R–positive, clinical considerations are different because surgery is undertaken not only with curative intent but also for palliation. Cytoreductive hepatic surgery sustains palliation of symptoms, reduces the need for additional treatment, and prolongs survival in selected groups of patients (*29,30*). Adjuvant strategies after liver resection may be of great value for patients with hepatic neuroendocrine tumors because (occult) residual tumor burden within the liver will be low after the resection. Of these patients with liver metastases of neuroendocrine tumors, 65%–75% have extrahepatic disease, as can be detected by scintigraphy (*30*). Development of effective adjuvant treatment after cytoreductive hepatic resection may make more patients eligible for surgery. The first finding from this study was that the growth of SS-R–positive pancreas carcinoma CA-20948 tumors was increased by PHx to the same extent as we found earlier for tumor CC531 (*5,11,31*). Therefore, our model with PHx seemed appropriate to investigate the effect of octreotide and PRRT on SS-R–positive and SS-R–negative tumors during accelerated growth. We did not find a reduction in tumor growth after PHx in our experiments using octreotide alone (*5*). However, we showed that PRRT with 370 MBq ^{111}In-DTPA^{0}-octreotide on days 1 and 8 significantly inhibited the growth of SS-R–positive CA-20948 tumors in the liver. After PRRT, only a few tumor colonies were present in sham-operated and PHx animals, whereas all control animals had a large tumor burden in their livers after 21 d. In previous studies on animals without PHx, we found that PRRT significantly decreased the growth of SS-R–positive tumors in the liver even when PRRT was performed 12 d after inoculation of the tumor (*10,31*). The necessity of the SS-R for this tumor growth–inhibiting effect was proven when blocking of the SS-Rs by pretreatment with octreotide (before PRRT) was shown to stop the effect of PRRT almost completely. Moreover, like the current study for sham-operated animals, the previous studies found no effect on SS-R–negative CC531 tumors. Three other experimental studies with radiolabeled SS analogs demonstrated the antiproliferative potential of PRRT on solid subcutaneously transplanted tumors, using ^{64}Cu-TETA^{0}-octreotide, ^{90}Y-DOTA^{0}, Tyr^{3}-octreotide, and ^{188}Re-RC-160, respectively (*32–34*). However, the effect of PRRT was never demonstrated for liver tumors. Recently, the first results of PRRT with ^{111}In-DTPA^{0}-octreotide in patients with neuroendocrine tumors were documented using a cumulative dose of 74 GBq. There were no major clinical side

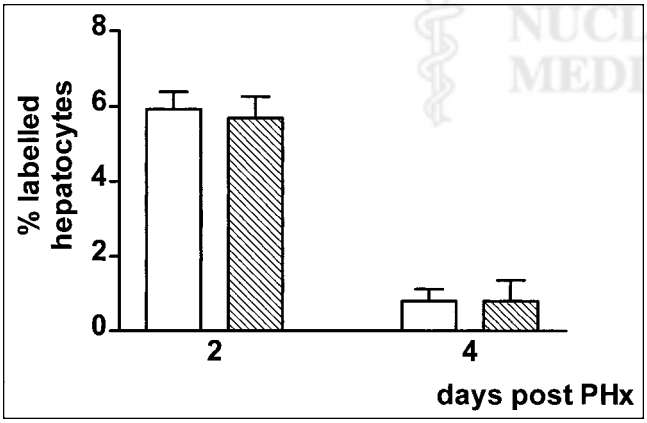

FIGURE 2. PRRT with ^{111}In-DTPA^{0}-octreotide and liver regeneration after 70% PHx. White bar = control; hatched bar = PRRT

effects, and there were promising beneficial effects on clinical symptoms, hormone production, and tumor proliferation. Of the 21 patients who received a cumulative dose of more than 20 GBq, 8 showed stabilization of disease and 6 others showed a reduction in tumor size (*35*).

In this study, we reconfirmed that PRRT has no significant effect on SS-R–negative CC531; therefore, no effect was expected after PHx. However, tumor growth was significantly reduced by PRRT after PHx also for this SS-R–negative tumor, albeit far less than observed for SS-R–positive tumors. It could be that liver regeneration is impaired by PRRT, as has been described for octreotide (*36*,*37*). This putative inhibition of regeneration could also lead to less tumor growth stimulation. Therefore, we investigated the effect of PRRT on liver regeneration in non–tumor-bearing animals. PRRT was given 1 d after PHx because liver regeneration is most profound during the first 48 h after PHx (*38*). The restoration of liver weight was not found to be affected. Both groups showed a fast increase in liver weight during the first few days after PHx. At different intervals up to 32 d, when complete restoration of liver volume is to be expected, no difference was found in wet liver weight. Also, no difference in BrdU labeling index was found, indicating that there was no difference in the number of regenerating hepatocytes. Functional recovery of the liver, studied by BSP clearance and basic liver function tests, was not significantly different. Therefore, we conclude that the decrease in tumor growth by PRRT after PHx was not caused by an inhibitory effect on liver regeneration. An explanation for the effect of PRRT on SS-R–negative tumors could be that the neovasculature of regenerating livers expresses a high density of SS-Rs, as has been demonstrated in peritumoral veins in primary tumors and their metastases (*39*,*40*). The effect of PRRT on these SS-R–negative tumors could then be ascribed to accumulation of the radionuclide close to the tumor cells and the effect on angioneogenesis.

CONCLUSION

This study demonstrates that PRRT can reduce increased tumor growth after PHx. This effect was strong for SS-R–positive tumors, probably mediated through the SS-R; however, also for SS-R–negative tumors, PRRT could reduce the increase in tumor growth. Liver regeneration is not impaired by PRRT, nor is the function of the remaining liver, implying that PRRT might be an effective clinical option after PHx.

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