Radioimmunotherapy and Fractionated Radiotherapy of Human Colon Cancer
Liver Metastases in Nude Mice

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ABSTRACT

Radioimmunotherapy (RIT) and radiotherapy (RT) were evaluated in nude mice developing liver metastases of human colon cancer. Without treatment, 90% of preconditioned nude mice, injected with LS174T cells intrasplenically and splenectomized, died between 26 and 93 days after grafting with few to several hundred liver metastases. RIT with 500 μCi of 131I-labeled anti-carcinoembryonic antigen monoclonal antibodies, injected i.v. in 3 weekly fractions, was initiated 1 to 3 weeks after grafting. Mean survival increase was 43 days for mice treated at 2 weeks. From 13 mice treated at 1 week, 8 mice showed long-term survival, a significantly better cure rate compared to RIT at 2 weeks. Mice undergoing RIT at 3 weeks showed similar survival as untreated controls. Mice injected with 131I-labeled irrelevant IgG1 or unlabeled antibody showed no significant survival increase. Conventional fractionated external beam RT of the liver showed that 40–50 Gy treatment initiated 1 week after grafting gave long-term survival in 7 of 13 mice, significantly better compared to RT at 2 weeks. With combined RIT + RT initiated 2 weeks after grafting, 5 of 11 mice had long-term survival in the absence of major toxicities. Thus, early RIT and RT were more efficient than later treatments, and combination therapy might give further improvement.

INTRODUCTION

The liver is frequently the first and unique site of dissemination of colorectal cancer; one explanation is that it functions as the initial filter of blood drained from the intestines. Because of a different tumor bed, an animal model of liver metastases from colorectal cancer should be more relevant to the clinical situation of patients with that disease than the commonly used s.c. tumor implantation site.

Liver metastases models are more complex than the s.c. one because they require a surgical intervention for tumor transplantation and also because engraftment frequencies are less predictable. Several reports have described the establishment of liver metastases from human colon cancer in severe combined immunodeficiency (SCID) or BALB/c nude mice (1–3). However, to our knowledge, RIT studies have not been performed in these mice. One RIT study was performed in mice with lung metastases obtained through i.v. injection of tumor cells (4).

Experimental RIT of solid tumors has shown that radiolabeled antibodies can produce tumor regression and sometimes cures when animals are treated early after transplantation (when tumor nodules are still small; Refs. 5 and 6) or with tumors that give exceptionally high antibody uptakes (7, 8). With other tumor lines that better reflect experimental PIT.

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3 The abbreviations used are: RIT, radioimmunotherapy; RT, radiotherapy; MAb, monoclonal antibody; CEA, carcinoembryonic antigen.

MATERIALS AND METHODS

Cell Line. The CEA-expressing human colon carcinoma cell line LS174T (20) was obtained from the American Type Culture Collection (Rockville, MD). This cell line is known to have a good potential for development of liver metastases when intrasplenically grafted in nude mice (21). Cells were grown as a monolayer in RPMI 1640 culture medium (Life Technologies, Inc., Paisley, United Kingdom) with 10% fetal calf serum and penicillin-streptomycin (Life Technologies, Inc.). For transplantation, cells in exponential growth were harvested using trypsin (0.05%)-EDTA (0.02%; Life Technologies, Inc.) and resuspended in serum-free RPMI. Sodium-heparinate solution was added at a final concentration of 1 IU/ml, and the single cell suspensions were kept on ice until use within 1.5 h.

Nude Mice and Pregrafting Treatment. Seven to 9-week-old female, outbred Swiss nude mice, homozygous nu/nu, produced at our institute, were used in accordance with Swiss guidelines for experimental animal research. Animals were kept under aseptic conditions and fed with standard vitaminated, irradiated food. Drinking water was supplemented with a polyvitamin preparation (Propovit M; Hoffman-La Roche, Inc., Basel, Switzerland) 1 ml/liter during 4 days of each second week.

As a pregrafting treatment, mice were given a single dose of 4 Gy (400 rad) total body irradiation 4 days before tumor grafting, using a 137Cs irradiator (dose rate, 1.85 Gy/min), and a single i.p. injection of 50 μg of rabbit anti-asialo GM1 antibody (Wako, Osaka, Japan) 1 day before grafting (19). This antibody suppresses the natural killer activity of nude mice (22).

Establishment of Liver Metastases. Pretreated mice were anesthetized with 250 μl of NaCl:ethanol (9:1) containing tribromoethanol (25.5 mg/ml; Aldrich Chemicals, Gillingham, United Kingdom) using i.p. injections, and the abdomen was prepared for sterile surgery. A small (5-mm) left subcostal incision was made, the spleen was isolated between strips of sterile gauze, and a single-cell suspension of 1 X 106 LS174T tumor cells in 0.05 ml RPMI-heparinate was slowly injected into the spleen, using a 0.45-mm needle. Three min after injection, the spleen vessels were ligatured, the spleen was resected, and the abdomen was closed with sutures. This protocol gave previously high numbers of liver metastases in the large majority (92%) of mice (19).

Monoclonal Antibodies. A pool of four intact mouse anti-CEA MAbs, (MAB 35, CE 25-B7, B93, and B17; Refs. 7 and 23), all of IgG1 subclass, was used for RIT. An irrelevant mouse IgG1 was used as control. The four anti-CEA MAbs are directed against four independent epitopes of CEA, Gold-2, -4, -1, and -3 (24), and have been or are being used in clinical studies (25, 26). MAbs were produced in vitro using the Technomouse apparatus (Integra-Biosciences, Tecnomona Fernwald, Germany) in the presence of at least 5% FCS and purified by ammonium sulfate precipitation and ion exchange chromatography (7).

Radilabeling of Anti-CEA MAbs and Control IgG1. Pooled anti-CEA MAbs and irrelevant control IgG1 were labeled using the iodogen method. Final specific activities were generally 4 (range, 3 to 6) μCi of 131I/μg of protein. Radiolabeled proteins were separated from free iodine by chromatography on Sephadex G-25 columns (Pharmacia Biotech, Inc.). Immunoreactivity was determined for all radiolabeled MAB preparations (27) in a direct binding assay on CEA insolubilized on CNBr-Sepharose (Pharmacia Biotech, Inc.). Binding of radiolabeled anti-CEA MAbs to CEA-Sepharose was 80.6 ± 3.0% and 1.2 ± 0.3% to control protein-Sepharose.

RIT. RIT was started from 1 to 3 weeks after intrasplenic tumor grafting. It consisted of three injections in the tail vein of 200, 150, and 150 μCi of 131I (about 50 and 35 μg protein, respectively) labeled intact anti-CEA MAbs (RIT group), with an interval of 7 days between injections. Control groups were injected either with the same doses of 131I-labeled irrelevant IgG1 or with the same amounts of unlabeled pooled anti-CEA MAbs, or were not injected.

The mean whole-body half-life of radiolabeled anti-CEA MAbs and control IgG1, measured by placing the mice three to four times per week in a dose calibrator, was for the different iodinations (injected each in four to seven mice) 93.3 ± 5.8 h (m ± SD) and 109.4 ± 11.2 h, respectively.

Method of External Beam Irradiation (RT). For RT, X-rays were generated by a Philips RT 250 apparatus operating at 200 kV and 20 mA. The beam was filtered with 0.5-mm copper (half-value layer, 1-mm copper). Up to three mice per irradiation were restrained in 3-mm lead jigs (28) designed with a lateral cutout of 23 x 17 mm to expose the upper abdomen of the mice (Fig. 1). The jigs were placed in a Perspex box with an additional lead shield with 30 x 19-mm openings. This set-up gives a minimum scatter to the animals placed at 52.5 cm from the source. The median dose rate was 0.69 Gy/min with a variation of ± 18% (0.82 Gy/min to skin at entry, and 0.58 Gy/min to skin at the distant side of the beam).

To obtain dose homogeneity, mice were irradiated alternatively from left and right using jigs with left or right openings.

The position of the irradiation window in the lead jigs was confirmed by quantitative liver scintigraphy performed 5 min after i.v. injection of 200 μCi of 125I-tc-colloidial albumin (Albu-Rex; Sorin Biomedica, Vercelli, Italy), which is rapidly taken up by the reticuloendothelial system, especially the liver and spleen. Nine mice were evaluated: three mice with liver metastases and six mice without. For the nine mice, using a pinhole collimator, planar scintigraphy was recorded first (for 2 min) with the unanesthetized mice restrained in the lead jig. The mice were then scanned a second time under anesthesia without the lead jig. As shown for a representative mouse (Fig. 2), the entire metastatic liver was visualized through the irradiation window of the lead jig, assessing its correct position and size. The scintigraphy is overexposed to show the extreme positions of the liver of the moving animal.

Quantitative measurement of radioactivity of the mice in the lead jigs (in the irradiation position) showed that 87 ± 7% of the total body radioactivity (measured outside the lead jigs) was recorded by the camera through the irradiation window. The mice were sacrificed at the end of scintigraphy, and whole-body radioactivity and that of the isolated liver were measured in a dose calibrator (Atomlab 100; Atomic Products Corp., Shirley, NY). Scintigraphic measures could thus be compared with the radioactivity counting in the dose calibrator that showed that 81 ± 4% of total body radioactivity was in the liver.

We concluded, therefore, that the entire liver of the mice restrained in lead jigs (without anesthesia) was facing the cutout during the 2-min image acquisition.

Radiotherapy. External beam RT was started 1 or 2 weeks after intrasplenic tumor grafting. Mice were given a weekly regimen of five fractions of 2 Gy over 5 days. RT was given alternatively from opposite sides to obtain dose homogeneity. Total doses of 20—50 Gy were given in 2—5 weeks.

Controls were not irradiated. A preliminary toxicity study was performed on nongrafted nude mice with the same irradiation protocol (total doses of 20 to 70 Gy were given in 2—7 weeks).

Combined Therapies. Based on the results from two other combined therapy studies (9), 4 RIT and RT were given simultaneously over 17 days. Treatment was started 2 weeks after grafting, with five fractions of 2 Gy RT given in 2.5 days. A first dose of RT, consisting of an i.v. injection of 150 μCi 131I-labeled anti-CEA MAbs, was administered immediately after this first RT block. Another 10 Gy of RT (five fractions/5 days) was started day 6, followed by the second injection of 150 μCi 131I-labeled MAbs. RT was concluded with 10 Gy (five fractions/5 days) started at day 13. Fig. 3 shows the timing of the combined therapy.

Endpoint Analysis of Therapies. Survival after 6 months was considered as a safe indication for mice that had either not developed metastases or that had been cured. All mice surviving at 6 months were sacrificed and autopsied. None of them had any nodule suspicious of tumor recurrence.

Survival increase in the therapy groups was calculated as mean survival

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number of mice that died, the χ² test was used to compare different groups. The overall survival curves after treatment, including death from metastases and long-term survival, were evaluated in the sense of a Kaplan-Meier survival analysis using the Lee-Desu comparison statistic.

RESULTS

In general, these experiments have been conducted in two blocks of 15 to 20 mice that were divided into three to five groups and always including a group of untreated mice. After completion of the experiments, concordant results were found in both experimental blocks, and results were pooled. Considering all control mice not receiving injections in the present study, 46 of 51 animals (90%) died with liver metastases between 26 and 93 days (mean, 46 days) after grafting, confirming the earlier observed engraftment frequency of 92% obtained under the same transplantation conditions (19).

Radioimmunotherapy. In three experiments, RIT was started 1, 2, or 3 weeks after grafting. Three injections, one time of 200 μCi and two times of 150 μCi of 131I-labeled anti-CEA MAbs, were administered with 7-day intervals.

Significant variation in the therapeutic effect, depending on the time of treatment initiation, was observed (Table 1). When mice were treated 1 week after grafting, long-term disease-free survival of 180 days was observed for 8 of 13 mice, whereas mice in the control groups of this experiment were all dead at 60 days (P < 0.01; Fig. 4A). At sacrifice 6 months after therapy, none of the surviving mice had any sign of remaining tumor.

When RIT was initiated at 2 weeks, prolonged survival was observed, but only 2 of 14 mice survived for 6 months without liver metastases (Fig. 4B). As compared to the therapy started at 1 week, the number of long-term survivors was significantly smaller (P < 0.02) in this therapy. Compared to the untreated control mice of this experiment, the mean survival increase of the other 12 mice was 43 days. When RIT was started at 3 weeks (Fig. 4C), no significant difference in survival was noted compared to untreated mice.

In the two experiments starting 1 or 2 weeks after grafting, only minor (not significant) differences in survival were found between the three different control groups that were not injected or had injection of unlabeled antibody or of radiolabeled irrelevant IgG1 (Fig. 4, A and B).

Radiotherapy. For RT of mice with liver metastases, a new irradiation setup was developed (Fig. 1). Whereas thermoluminescent dosimeters were used for dose calibration, liver scintigraphy of unanesthesized mice restrained in lead jigs was used to define the precise position and size of the irradiation window (Fig. 2).

Fractionated RT (2 Gy/fraction/day, five fractions/week) to the liver was started 1 or 2 weeks after grafting using total doses of 20, 30, 40, or 50 Gy. A dose-dependent effect on survival was observed (Fig. 5). In the mice treated at 2 weeks, only a small survival increase compared to untreated mice was found after 20 or 30 Gy RT (Table 2). The response was significantly increased after RT of 40 Gy (P < 0.05 compared to 0 or 20 Gy) or 50 Gy (P < 0.05 compared to 0, 20, or 30 Gy). In this experiment, only 2 mice of 39 have shown

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\[5 \text{ Due to a technical problem, mice of the combined therapy experiment did not have this last measure.}\]
long-term survival and can be attributed to the 10% of grafted mice that statistically do not develop liver metastases.

In mice treated at 1 week after grafting, long-term survival without evidence of tumor in 7 of 13 mice was observed after 40–50 Gy RT, which represents a significant improvement compared to only 1 mouse with long-term survival of 14 mice in RT at 2 weeks (P < 0.01).

**Combined Therapy.** Fig. 6 shows the survival curve of mice treated by combined RIT (2 × 150 μCi of 131I-labeled MAbs and RT (30 Gy in 15 fractions). Therapy was initiated 2 weeks after grafting. Disease-free survival of 180 days was observed for 5 of 11 mice after the combined therapy, whereas the majority of the mice (8 of 10) were dead at 60 days in the untreated control group. In the two other control groups treated with RIT or RT alone, 6 of 7 and 6 of 6 mice, respectively, were dead at 79 days. At sacrifice 6 months after therapy, none of the surviving mice had any sign of remaining tumor. The combined treatment initiated at 2 weeks after grafting shows an interesting cure rate of 45%, which does not, however, reach significance compared to the number of long-term survivals in the other groups. When survival increase was analyzed by the Lee-Desu comparison, the combined therapy showed a significant improvement (P < 0.05) compared to RIT or RT alone or to untreated mice.

**Toxicity of the Treatments.** Several types of toxicity were observed as side effects of RIT or RT; hematological toxicity and weight loss were observed after RIT, and late local skin toxicity, ascites, and death were observed after high-dose RT.

Hematological toxicity (Table 3) occurred in mice treated with radiolabeled MAbs. Petechiae were observed in 10 of 34 mice treated with total doses of 500 μCi of 131I-labeled MAbs. Petechiae were observed 7 to 14 days after the last injection and disappeared about 1 week later. No petechiae were observed in the other treatment groups, including the combined RIT + RT. A blood analysis was performed 10–12 days after either the last injection of radiolabeled MAbs or after the last RT. An important depression of peripheral WBCs was found after RIT alone or after combined RIT + RT. Peripheral WBCs were less depressed after RT alone. In mice treated with 500 μCi of RIT, a relatively moderate platelet depression was observed, despite observation of petechiae, with a large scatter of counts. Because of a technical problem, platelets could not be counted in the experiment of combined RIT + RT. However, the absence of petechiae in this group is a good indication of a moderate platelet depression. Mice injected with a radiolabeled irrelevant IgG1 had a more important blood cell depression than mice injected with radiolabeled anti-CEA MAbs, but about the same proportion of mice had petechiae (Table 3). This might be due to the longer half-life of the irrelevant IgG1 (109 ± 11 h) compared to anti-CEA MAbs (93 ± 9 h). Weight loss after RIT was generally modest, and mice completely recovered by 14 days after last injection.

Peak local skin toxicity after RT was analyzed in an experiment with nongrafted nude mice (Table 4). It could not be evaluated in mice bearing liver metastases, because most of these animals died before development of this late toxicity. Following irradiation with doses of 40–70 Gy, grades I and II skin toxicity were observed. Skin toxicity appeared about 2 months after treatment initiation, and healing was observed after an additional 5–6 weeks. Four mice died from late toxicity about 3 months after 50–70 Gy RT completion (Table 4). All of these mice had ascites at autopsy. The surviving mice were sacrificed 6 months after first irradiation, without evidence of any disease.
In all of these experiments, death in the absence of liver metastases occurred in 13 of a total of 191 grafted mice (7%). Three of these mice (1 after RT, 1 after injection of unlabeled MAbs, and 1 untreated) had abdominal tumors but none in the liver. For the other 10 mice (5%), no tumor was found at autopsy, and death was not specifically related to a certain treatment. These deaths can probably be attributed to the overall fragility of nude mice that have been observed here over 6 months. The fact that these deaths occurred in all groups, irrespective of the treatments (four times after RTT, two times after 131I-labeled control IgG1 injections, two times after RT, once after RT + RT combined, and once for an untreated control mouse), supports this hypothesis.

**DISCUSSION**

Nude mice bearing established liver metastases from human colon cancer were treated by systemic RTT and/or by fractionated external beam RT. By using intact MAbs for RTT in mice, a low radiation dose rate was obtained, comparable in intensity to the dose rate that can be obtained in patients injected with high doses of 131I-labeled intact MAbs or F(ab')2 fragments.

The effect of RTT on tumor was dependent on the time of treatment initiation, i.e., dependent on the size of the liver metastases at first antibody injection. When initiated 1 week after grafting, a significant number of probable cures was observed with 8 of 13 mice showing tumor-free survival after 6 months. RTT initiated 2 weeks after grafting produced a significant survival increase compared to untreated controls, but the number of long-term survivors was in the range of background. Interestingly, no substantial survival increase was observed in mice treated 3 weeks after grafting.

These results are remarkable concerning several aspects. It has been calculated that RTT with 131I-labeled MAbs should be most efficient for therapy of tumor nodules of 1–5 mm in diameter (29–32). Our results, however, indicate that the best result was obtained in mice with tumors that probably never reached the size of 1 mm in diameter. Indeed, we have shown that these liver metastases, even after unlimited growth for 3 weeks, were frequently of less than 1-mm size. Furthermore, a preliminary experiment has shown that only three of five mice sacrificed 1 week after grafting had very small liver nodules of about 0.5 mm in diameter.
In the same series, two of four mice sacrificed at 2 weeks had nodules of maximally 1.5 mm in diameter, whereas the two other mice presented tumors of maximally 2.5 and 4 mm in diameter, respectively. Our results, therefore, extend earlier observations in mice with s.c. tumors (5, 6, 8) or with lung metastases (4), showing that very small tumor nodules are easier to treat than larger ones.

It is well accepted that the absorbed dose of β-radiation of uniformly distributed 131I diminishes in very small tumors. If this β-radiation is almost completely absorbed by tumors of 3-4 mm in diameter, 54% of radiation would be absorbed in nodules of 0.5 mm in diameter, and only 17% in nodules of 0.1 mm in diameter (29). Furthermore, it is well known that conventional RT of large tumor masses is less efficient than that of smaller tumors; one reason is that the number of clonogenic cells is correlated with tumor size. Whereas tumors of 1 cm in diameter represent about 10^9 cells and tumors of 1 mm about 10^6 cells, such tumors can be sterilized by 60-70 Gy and 40-45 Gy, respectively. Nodules of 0.1 mm in diameter, however, represent about 10^5 cells that can be sterilized by about 20-23 Gy (33). Thus, the decrease of absorbed dose in smaller nodules is partially counterbalanced by the reduction of radiation dose needed for sterilization. As a result from these two contradictory radiobiological rules, it has been shown that spheroids of 0.03 mm radius would require the double amount of 131I per mass unit compared to spheroids of 1-mm radius to reach the same tumor control probability (30).

The mentioned radiobiological calculations assume that radiolabeled MAb distribution within tumors is homogeneous and that the radiosensitivity of cells within a given tumor is constant. However, several additional aspects of RT might further explain the striking effect on very small tumor nodules that has been observed here with 131I-labeled MAbs: (a) antibody uptake can be higher in small tumor nodules than in larger ones (8, 19, 34) and can be very high in small clusters of tumor cells (35, 36); (b) it has been shown that significant numbers of blood vessels develop as early as 4 days after s.c. tumor inoculation in nude mice and that small tumor transplants, irrespective of whether the tumor bed is well or poorly vascularized, show good blood perfusion (37). This would allow cycling of all cells in very small nodules and correlate with a high radiation sensitivity; (c) suboptimal distribution of intact MAbs on the surface of large nodules might be responsible for insufficient irradiation of deeper parts of such tumors. Indeed, it has been shown that 131I-labeled MAbs, incubated up to 90 h with LS174T spheroids, did not penetrate deeper than a few cell layers (38). For larger tumors (2 or 3 weeks after transplantation in the present study), nonhomogeneous antibody distribution in tumor, which could reduce efficiency of RT to 65% (39), as well as hypoxic and radioreistant cells could explain the relative failure of RT. This situation might also exist in our experiments despite the fact that we used fractionation RT with the aim of obtaining a "peeling off" effect.

It has been suggested that RT should be evaluated in minimal disease, despite the absence of demonstrated effectiveness on large tumor masses. Indeed, successful prolonged survival has been reported in patients with minimal residual disease after i.p. injection of radiolabeled MAbs (11). Support for such a therapeutic approach has been based on the fact that delivery of radiation by large proteins, such as antibodies, is particularly ineffective in large tumor masses, as has been shown repeatedly (32). Our results obtained 3 weeks after grafting dramatically illustrate this consideration. RT that was very efficient and even curative when initiated 1 week after grafting did not give any measurable effect when initiated 3 weeks after grafting. Lower overall mean antibody uptake, unfavorable histological distribution of antibody in tumor, as well as hypoxia and radioreistance of noncycling tumor cells might all have contributed to this poor result on the larger tumor nodules.

External beam RT initiated 2 weeks after grafting, at different dose levels, showed a direct correlation between survival increase and RT dose. RT of 20 or 30 Gy gave only a minor survival increase, whereas a significant increase was observed at 40 and 50 Gy. No significant numbers of cures could be obtained, however, confirming the relative radioreistance of this tumor that has been observed previously (9, 10). When starting RT 1 week after grafting, a significant number of mice showed long-term survival after 40-50 Gy total doses without any evidence of tumor at 180 days. This is a further demonstration that RT covered the whole liver in these mice and confirms that RT efficiency is better for small tumor nodules than for larger ones.

For the combination of RT and RT, lower doses compared to single treatment modalities have been used to minimize possible additive toxicity. This combination revealed an interesting tendency of increased numbers of long-term survivors compared to untreated controls and single modality treatments at 2 weeks after grafting. An additive therapeutic effect of RT and RT on this same tumor, transplanted s.c., has been observed previously (9). Although the 90% overall liver engraftment frequency observed here can be considered as quite successful, larger groups of mice would be needed to obtain significant results on cure rates in the range of 10-50%.

Concerning toxic side effects, we did not observe any skin toxicity for the RT doses that were used here in grafted mice. Hematopoietic toxicity was demonstrated for RT alone as well as for the combined therapy. Unfortunately, the field of RT in these mice was quite large, so that the potential for combination therapy was limited by the fact that several important organs and a large part of the bone marrow were in the irradiation field of RT.

Antibody-dependent, cell-mediated cytotoxicity or complement-dependent cytotoxicity and possibly antibody-induced apoptosis are probably at the origin of the efficacy of unlabeled antibody therapy of B-cell lymphomas (40). For carcinoma, however, the injection of unlabeled MAb in nude mice has not been able to induce regression of well-established tumors but only inhibited the engraftment of various tumor lines when MAb injection was performed 1-2 days after grafting (41). Therapy with unlabeled antibody has, nevertheless, found an application in an adjuvant setting after successful surgical removal of solid tumors, showing promising results in one study (42).

In our experiments with solid tumors, the survival increase obtained in mice injected with unlabeled anti-CEA MAbs was marginal. It is possible that antibody-dependent, cell-mediated cytotoxicity or complement-dependent cytotoxicity still play a role in elimination of the last, potentially clonogenic, cells that could remain after RT.

In conclusion, we have shown here that RT using 131I-labeled MAbs is able to destroy colon cancer micrometastases at an early stage, leading to a cure of more than 60% of mice that would otherwise die from liver metastases. We have further shown that RT of human colon cancer liver metastases can be studied in an experimental model with a clinically relevant fractionation schedule, and that RT initiated at 1 week gives a...
higher percentage of long-term survival than RT delayed for an additional week. The combination of RT and RT opens an interesting perspective for treatment of such disease in patients. A clinical feasibility study of combined RT + RT of patients with liver metastases from colorectal cancer has been initiated.

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