Intratumoral Injection of Rhenium-188 Microspheres into an Animal Model of Hepatoma

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Intratumoral injection of ^{90}Y microspheres is a potential alternative in the treatment of primary liver tumor. However, complicated preparation and lack of a gamma ray for imaging are the disadvantages of ^{90}Y. In this study, we used ^{188}Re, a generator-produced radioisotope with 155-keV gamma ray emission, to label microspheres. After intratumoral injection of ^{188}Re microspheres into rats with hepatoma, biodistributions and survival times were analyzed. **Methods:** Twelve male rats with hepatoma were killed at 1, 24 and 48 hr (4 rats at each time point) after intratumoral injection of ~7.4 MBq ^{188}Re microspheres. Samples of various organs were obtained and used to calculate the tissue concentrations. In addition, 30 male rats bearing hepatoma were divided into two groups (15 rats in each group) to evaluate survival time. Group 1 received intratumoral injection of 37 MBq ^{188}Re microspheres, whereas Group 2 served as the control group and received an intratumoral injection of 0.1 ml normal saline only. Survival time was calculated from the day of injection to 2 mo after treatment. **Results:** Radioactivity in the tumor was very high throughout. Biological half-time was 170.8 hr. Radioactivity in the lung was 1.78% injected dose (ID)/g at 1 hr but declined rapidly over time. The concentration in the urine was ~6.14% ID/ml after the first hour and rapidly declined thereafter. The concentrations of radioactivity in other organs, such as normal liver, muscle, spleen, bone, testis and whole blood, were quite low throughout the study. Twelve of 15 (80%) of rats survived over 60 days after intratumoral injection of ^{188}Re microspheres, whereas only 4 of 15 (26.7%) survived more than 60 days after injection of normal saline only. The difference between the groups was significant ($p < 0.05$). **Conclusion:** Rhenium-188 offers cost-effectiveness, on-site availability, short half-life, energetic beta particle, emission of gamma photons for imaging, easy preparation, easy clinical administration and apparent lack of radiation leakage from the treated tumor. Direct intratumoral injection of ^{188}Re microspheres is extremely attractive as a clinical therapeutic alternative in hepatoma patients.

Key Words: rhenium-188; microsphere; intratumoral injection; hepatoma; biodistribution

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Hepatocellular carcinoma (HCC) is one of the most common tumors in the world. Its incidence is increasing in Europe and Africa, but HCC is already a major health problem in Asia. In Taiwan, HCC ranks first for men and second for women as a cause of cancer death.

The only curative therapy for HCC is surgical resection. Despite improved diagnosis as a result of better imaging and screening programs in certain parts of the world, the number of patients eligible for curative surgery remains small and is seldom more than 10%–15% of the total patient population. Thus, the majority of patients require a multidisciplinary approach to management.

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External-beam irradiation is limited because of normal liver intolerance to radiation and low radiation dose to tumor. Selective internal radiation (hepatic arterial targeting therapy with radioisotope) seems to be an attractive alternative, as it provides a higher radiation dose specifically to the liver tumor (*1–5*). There are two isotopes, ^{90}Y and ^{131}I, that are currently used for selective internal radiation by intrahepatic artery injection. Yttrium-90 is usually tagged to a resin base or glass microsphere, and ^{131}I is usually administered in conjunction with lipiodol. Selective internal radiation with ^{131}I-lipiodol has been shown to deliver an adequate tumoricidal dose of radiation to HCC (*6*). However, this method has some inherent drawbacks (*7,8*). Yttrium-90 has several advantages over ^{131}I, including a shorter half-life and a longer beta energy range. In 1994, we successfully labeled lipiodol with ^{90}Y (*9*).

Rhenium-188 has similar beta energy characteristics to ^{90}Y, with many advantages, such as generator production, a shorter half-life than ^{90}Y and the emission of 155-keV gamma rays for tumor imaging. In 1995, we successfully labeled lipiodol with ^{188}Re (*10*) and obtained promising results after intrahepatic arterial injection into rats with hepatoma.

Direct injection of ^{90}Y glass microspheres into hepatoma was used by Tian et al. (*11*). However, the preparation of ^{90}Y glass microspheres is labor intensive. In this study, we labeled microspheres with ^{188}Re and evaluated the efficacy of intratumoral injection of ^{188}Re microspheres for hepatoma in rats.

MATERIALS AND METHODS

Rhenium-188 Production

Rhenium-188 was obtained from an alumina-based $^{188}W/^{188}Re$ generator. Tunsten-188 was supplied by the Oak Ridge National Laboratory (Oak Ridge, TN) and was produced by double-neutron capture of W-186. Elution with normal saline provided solutions of carrier-free ^{188}Re-sodium perrhenate ($NaReO_4$) from the $^{188}W/^{188}Re$ generator (*12–14*). High-performance liquid chromatographic analysis revealed that the ^{188}Re eluate was >99% perrhenate. Tungsten-188/^{188}Re generators have demonstrated consistently high ^{188}Re yields and low parent breakthrough for periods of at least 2 mo.

Preparation of Rhenium-188 Microspheres

Rhenium-188 (148 MBq) was added to 20 mg vacuum-dried microspheres (Aminex A-27; Bio-Rad, Richmond, CA) and mixed with a mixer for 15 min. $SnCl_2$ anhydride (200 mg) and 1 ml of 0.2 *N* HCl were added, and the solution was mixed again for an additional 5 min. The contents were boiled on a hot plate for 30 min and then centrifuged. After centrifugation, the supernatant was removed. Vials of ^{188}Re microspheres were reconstituted as required by resuspension in an aliquot of normal saline.

In Vitro Stability Test

Aliquots of ^{188}Re microspheres were added to tubes containing an equal volume of pooled human serum at 37°C. The tubes were stoppered and mixed continuously on a rotator. At 5 hr, 1 day, 2

TABLE 1
Mortality and Pharmacotoxic Symptoms of Sprague–Dawley Rats After Intraperitoneal Injection of Normal Saline, Aminex and Rhenium-Aminex

Dose	Mortality and pharmacotoxic symptoms	
	Male rats	Female rats
1000 mg/kg rhenium-Aminex	One mortality, two rhinorrhea, two loose stool, one lethargy and ataxia and one dehydration	Two mortalities, one rhinorrhea, two lethargy and low body temperature, two dehydration, two distention of abdomen and one abnormal urination
≤300 mg/kg rhenium-Aminex	No toxicity symptoms	No toxicity symptoms
Normal saline	No toxicity symptoms	No toxicity symptoms
1000 mg/kg Aminex	No toxicity symptoms	No toxicity symptoms

days and 3 days, the tubes were removed and centrifuged at 500 × g for 5 min. Aliquots of the supernatants were counted by a gamma counter, and the precipitate was readjusted to original volume and returned to the rotator. All counts were corrected for radioactive decay and expressed as a percentage of the total radioactivity measured at the beginning of the experiment.

Toxicity Studies of Rhenium Microspheres

The acute toxicity study of the commercial rhenium microsphere product (Remicrosphere) was performed using Sprague–Dawley (SD) rats. The rats were divided into five groups (5 male and 5 female rats per group) and intraperitoneally injected with 0 (normal saline only), 100, 300 or 1000 mg/kg Remicrospheres or 1000 mg/kg microspheres. The rats were observed for mortality and pharmacotoxic signs at approximately 1, 2, 3 and 4 hr after administration and once daily for 14 days after a single-dose administration. Individual body weights were determined immediately before injection and then at Days 2, 3, 4 and 8 during the course of the study and again for survivors at the termination of the study.

Animals and Tumor Cell Line

Male SD rats weighing 200–250 g were fed a standard chow diet and were given water ad libitum. An N1-S1 hepatoma cell line (American Type Culture Collection, Manassas, VA) was used for tumor implantation. The tumor cells were routinely cultured in Dulbecco's modified Eagle's medium (Life Technologies, Inc., Paisley, United Kingdom) mixed with 5% fetal bovine serum, 1% L-glutamine and 20% horse serum. After growing exponentially for 1 wk, a concentration of approximately 4×10^6 cells per ml was established. The cell viability was over 90%, as determined by trypan blue exclusion.

Inoculation

A subxyphoid laparotomy, 1.5–2 cm long, was performed to expose the left and right lobes of the liver. Using a 27-gauge needle, a tumor cell suspension containing 4×10^6 cells in a volume of 0. 1 ml was injected slowly into one of the hepatic lobes under the liver capsule, raising a visible pale wheal. The puncture site was gently compressed for 15 sec with cotton gauze to prevent bleeding. Then, the wound was closed in layers. Ten days after inoculation, sonography was performed again to check tumor growth.

Biodistribution

Twelve rats bearing liver tumor were used to determine the tissue biodistribution of ^{188}Re microspheres. Under anesthesia by intraperitoneal injection of ketamine, midline laparotomy was performed. After the hepatic tumor was exposed, 7.4 MBq (0.2 mCi) ^{188}Re microspheres in a volume of 0.1 ml were injected directly into the center of the tumor. The puncture site was gently compressed for 60 sec with cotton gauze to prevent bleeding. The rats were killed at 1, 24 and 48 hr (4 rats at each time point) after intratumoral injection. Samples (~0.1 g) of tumor, normal liver, spleen, muscle, lung, kidney, bone and testis were taken and weighed carefully. In addition, 1 ml whole blood and 0.5 ml urine were drawn from the heart and the urinary bladder, respectively. Radioactivity levels were measured by a well scintillation gamma counter (Packard Cobra), and tissue concentrations were calculated and expressed as percentage injected dose per gram (%ID)/g.

Calculation of Absorbed Doses

Tissue concentrations (%ID/g) were converted to human organ contents using the %ID-kg/g equivalence suggested by Kirschner et al. (*15*). All data were fit to one- or two-compartment exponential functions. Residence times (*16*) were calculated for various organs and the remainder of the body based on the observed retention curves. The residence time for the urinary bladder was calculated using the dynamic bladder model of Cloutier et al. (*17*). All residence times were entered into the MIRDOSE Version 3.1 computer program (*18*) to obtain estimates of the doses to individual organs.

Monitoring and Follow-Up

Thirty male rats bearing hepatic tumor were divided into two groups to evaluate the efficacy of treatment. Group 1 was comprised of 15 rats that received intratumoral injection of 37 MBq (1 mCi) ^{188}Re microspheres. The other 15 rats received intratumoral injection of 0.1 ml normal saline and served as the control group (Group 2). Tumor size was measured by liver sonography, Acuson 128×P computed sonography before injection and at 2 and 4 wk after injection. The maximum length and width of the lesion were measured by the same experienced ultrasound physician using the same machine. Survival time was calculated from the day of treatment to 2 mo after treatment by the life-table method, and the Wilcoxon test was performed for statistical analyses using a computer program (*19,20*). The response to treatment was classi-

TABLE 2
Tissue Distributions of Rhenium-188 Microspheres in Rats with Liver Tumors

Time (hr)	Tissue biodistribution (mean ± 1 s.d.), ID/g									
	Tumor	Liver	Lung	Kidney	Bone	Muscle	Spleen	Testis	Urine	Blood
1	21.16 ± 5.25	0.23 ± 0.06	1.78 ± 0.74	0.52 ± 0.03	0.05 ± 0.02	0.02 ± 0.01	0.16 ± 0.03	0.03 ± 0.04	6.14 ± 2.32	0.31 ± 0.08
24	18.74 ± 3.17	0.06 ± 0.01	0.46 ± 0.12	0.49 ± 0.21	0.03 ± 0.01	0.01 ± 0.00	0.02 ± 0.00	0.01 ± 0.00	0.68 ± 0.16	0.02 ± 0.00
48	17.16 ± 2.56	0.04 ± 0.02	0.22 ± 0.04	0.62 ± 0.15	0.02 ± 0.01	0.01 ± 0.00	0.02 ± 0.01	0.01 ± 0.00	0.16 ± 0.04	0.01 ± 0.00

TABLE 3
Estimated Doses (mGy) to Various Tissues in Rats with Hepatoma After Intratumoral Injection of Rhenium-188 Microspheres

Tissue	Dose (mGy/MBq)
Tumor*	636
Liver	1.22
Lung	0.253
Kidney	0.164
Spleen	0.019
Testis	0.0007
Muscle	0.0006
Red marrow	0.126
Bone surface	0.008
Urinary bladder wall	1.61

*Tumor was assumed to be ~2 cm in diameter.

fied according to the survival time and change in tumor size from pretreatment to 4 wk after treatment, as follows:

1. Good response, tumor size decreased;
2. Poor response, any condition less than good response or a survival time of <60 days.

RESULTS

In vitro stability tests revealed that the labeling efficiency of ^{188}Re microspheres was >90% over a 3-day period. The results of the acute toxicity study are shown in Table 1. No toxicity symptoms were observed in the groups that received doses of Remicrosphere under 300 mg/kg or in the groups that received microspheres or normal saline. In the group that received 1000 mg/kg Remicrosphere, observed mortalities were 20% for male and 40% for female rats. Clinical signs in the high-dose group included lethargy, ataxia, rhinorrhea, loose stool, abnormal urination, low body temperature, distention of abdomen and dehydration. The estimated acute intraperitoneal LD_{30} value of Remicrosphere in SD rats is 1000 mg/kg body weight.

The results of the biodistribution study of rats with hepatoma, expressed as %ID/g tissue, are summarized in Table 2. Our data show that the radioactivity in the tumor was very high throughout this study. The biological half-time was 170.8 hr. Radioactivity in the lung was 1.78%ID/g at 1 hr but declined rapidly over time. The concentration in the urine was about 6.14%ID/ml after the first hour and declined rapidly thereafter. The concentrations of radioactivity in other organs, such as normal liver, muscle, spleen, bone, testis and whole blood, were quite low throughout the study. The estimated doses of radiation to various organs are shown in Table 3.

Table 4 shows detailed data from the 30 rats studied for treatment effects and survival times. In the treated group, 10 rats showed good response to the treatment (Fig. 1). Complete disappearance of tumor was noted in 3 rats (Fig. 2). Five rats showed poor response to treatment, including 3 rats that died during this study and 2 other rats with good response in the second week but with tumor rebound in the fourth week. In the control group, the response to normal saline was poor in all 15 rats. Twelve of 15 (80%) rats survived over 60 days after intratumoral injection of ^{188}Re microspheres, whereas only 4 of

TABLE 4
Detailed Data of Control Group and Rats with Hepatoma After Intratumoral Injection of Rhenium-188 Microspheres

Rat no.	Tumor size (mm × mm)			Response	Survival time (days)
	Before	2 wk	4 wk		
1	18.3 × 22.3	8.8 × 11.3	10.5 × 15.6	Poor	>60
2	19.8 × 18.6	8.6 × 11.3	5.0 × 7.7	Good	>60
3	14.3 × 19.6	8.6 × 9.8	Disappeared	Good	>60
4	15.6 × 22.1	8.6 × 13.3	Disappeared	Good	>60
5	20.2 × 24.8	22.8 × 25.5	—	Poor	25
6	17.7 × 22.1	15.3 × 22.0	11.8 × 17.3	No	>60
7	15.7 × 18.3	8.0 × 10.0	5.1 × 6.1	Good	>60
8	18.8 × 23.6	13.5 × 18.6	4.1 × 5.1	Good	>60
9	20.0 × 23.2	7.1 × 14.8	3.6 × 6.8	Good	>60
10	16.7 × 24.4	11.1 × 13.3	6.0 × 9.8	Good	>60
11	22.2 × 22.8	—	—	Poor	10
12	16.0 × 23.5	8.3 × 9.1	7.0 × 10.1	Poor	>60
13	20.8 × 26.3	18.2 × 21.3	—	Poor	39
14	16.7 × 19.3	12.6 × 15.6	7.8 × 8.6	Good	>60
15	16.4 × 24.1	12.2 × 14.0	Disappeared	Good	>60
Control					
1	15.0 × 25.8	20.0 × 30.5	—	Poor	15
2	18.3 × 24.0	17.6 × 23.1	—	Poor	25
3	17.7 × 21.3	—	—	Poor	11
4	19.0 × 23.3	19.9 × 33.5	20.9 × 35.8	Poor	>60
5	22.3 × 19.0	—	—	Poor	12
6	18.7 × 20.3	26.1 × 31.4	—	Poor	17
7	20.4 × 25.0	24.3 × 28.3	—	Poor	12
8	18.6 × 25.5	25.9 × 26.5	29.8 × 37.0	Poor	40
9	19.1 × 23.0	17.3 × 19.7	—	Poor	20
10	18.6 × 20.7	—	—	Poor	11
11	19.4 × 21.6	18.9 × 30.2	14.5 × 24.4	Poor	>60
12	15.0 × 24.7	19.1 × 33.8	21.9 × 33.0	Poor	>60
13	15.7 × 23.0	16.5 × 22.5	17.8 × 30.7	Poor	>60
14	14.8 × 22.5	—	—	Poor	9
15	17.8 × 19.0			Poor	14

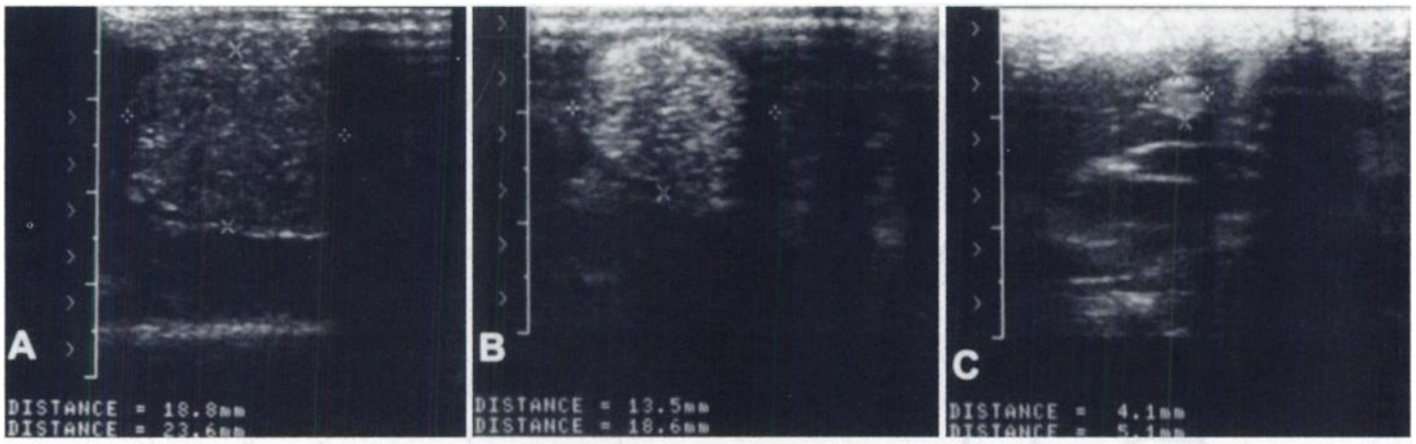

FIGURE 1. Tumor size of Rat 8 measured by sonography at the following intervals: (A) before treatment and (B) in the second and (C) fourth weeks after intratumoral injection of 37 MBq ^{188}Re microspheres. Tumor size decreased significantly after treatment.

15 (26.7%) controls survived >60 days (Fig. 3). The difference was significant ($p < 0.05$).

Gamma camera imaging clearly showed localization of ^{188}Re microspheres in the tumor 1 hr after injection and no significant leakage of ^{188}Re microspheres from the tumor in the 48 hr following (Fig. 4).

DISCUSSION

In previous reports of regional intra-arterial administration of radiolabeled ^{131}I-lipiodol or ^{90}Y microspheres, selective internal radiation as a single modality could deliver a tumoricidal dose of radiation to a hepatic tumor without jeopardizing nontumorous liver tissue (*21,22*). Several study series have shown that selective internal radiation is practical and feasible (*1–5*). However, intra-arterial infusion of radionuclides has some disadvantages. First, the radionuclide reaches the tumor site by a nonspecific route. This means that normal tissue would be irradiated in the same way as the tumor. Second, because of the nonspecific distribution, large quantities of radionuclides must be used. Third, this technique requires extremely selective catheterization and is, therefore, highly dependent on operator skill and equipment. Fourth, with the common existence of arteriovenous shunts in HCC, systemic leakage of radionuclides to the lung is very likely. Tian et al. (*11*) directly injected ^{90}Y glass microspheres into the tumor under real-time ultrasound guidance and obtained very encouraging results. Yttrium-90-glass microspheres were obtained by neutron activation of stable ^{90}Y that had been integrated into glass microspheres. The preparation of ^{90}Y glass microspheres is technically complicated and time consuming. In addition, lack of r-ray emission makes tracing the Y-90 radiopharmaceutical difficult.

Rhenium-188 is a very attractive radioisotope that is obtained from a ^{188}W/^{188}Re generator in a carrier-free form on a daily basis (*23*). The ^{188}W parent has a half-life of 69 days, which means that such a generator would have an extended useful life span for providing ^{188}Re. The availability of a generator for ^{188}Re permits the on-site "milking" of the radioisotope, in the same fashion as with ^{99m}Tc. The short half-life can also effectively reduce the problem of radiation waste. In addition, the labeling of microspheres with ^{188}Re is quite easy. The

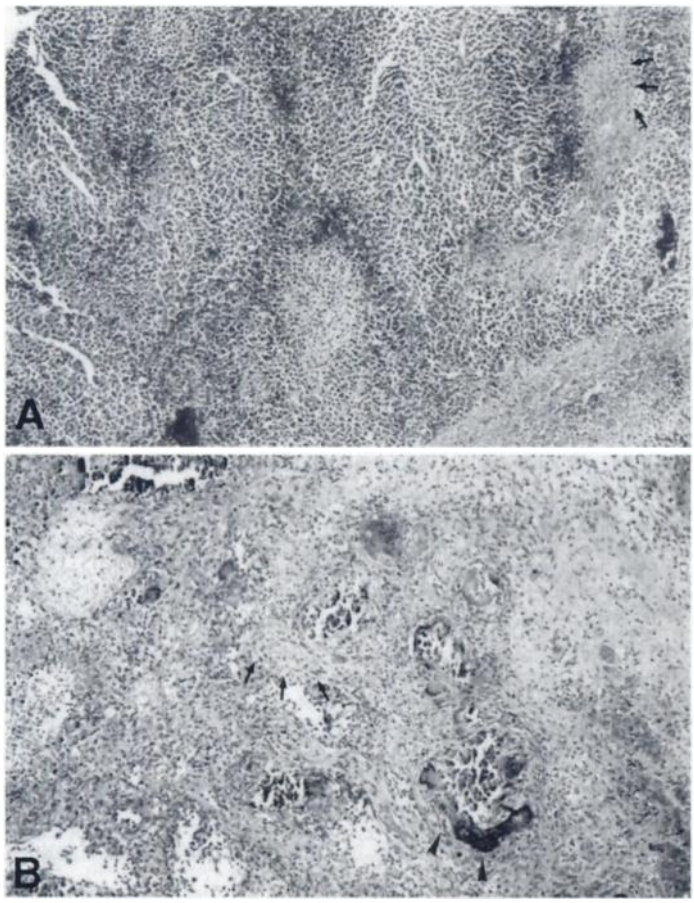

FIGURE 2. Effect of ^{188}Re microsphere treatment. (A) Before treatment, tumor shows hypercellular neoplastic cells with increased nuclear-to-cytoplasm ratio, pleomorphism and focal necrosis (arrows). (B) Two months after direct intratumoral injection of ^{188}Re microspheres, tumor was replaced by dense fibrosis (arrows) with focal foreign body granuloma containing multinucleated giant cells (arrowheads). No residual neoplastic cells were found.

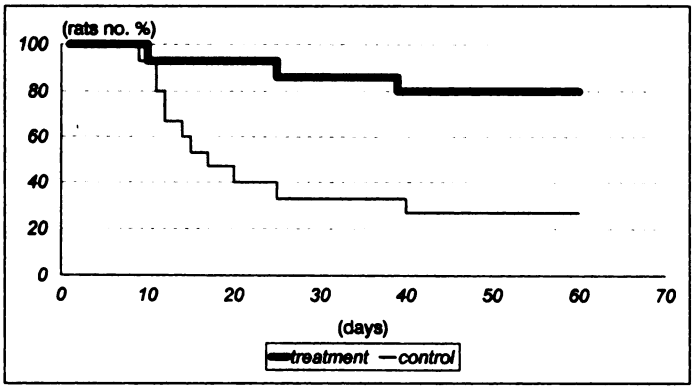

FIGURE 3. Survival curves for rats with hepatoma receiving intratumoral injection of ^{188}Re microspheres and control rats receiving only normal saline. The difference is significant ($p < 0.05$).

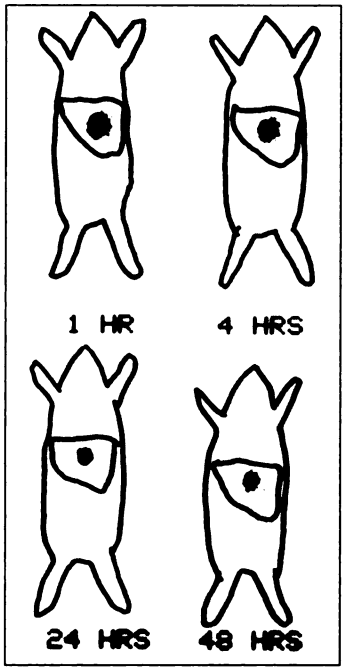

FIGURE 4. Scintigraphy was performed using large-field-of-view gamma camera with high-resolution collimator and an energy window of 135–175 keV. Images show localization of ^{188}Re microspheres in tumor 1 hr postinjection and no significant leakage of ^{188}Re microspheres from tumor in following 48 hr.

microsphere used in this study was an anion-exchange resin (acetate form) with a particle size of 15 ± 2 um. The acute toxicity study showed that the intraperitoneal LD_{30} for rhenium microspheres in SD rats is 1000 mg/kg. No symptoms of toxicity were recorded in SD rats receiving intraperitoneal injections of <300 mg/kg. The dose of microspheres will be only 0.86 mg/kg, far below the toxic dose, when a dose of 370 MBq ^{188}Re microspheres (100 mg microspheres) is administered to a 60-kg adult. On the basis of our study, microspheres are very stable and low in toxicity. However, a chronic toxicity study should be performed before application to humans.

Biodistribution showed that ^{188}Re microspheres, after direct intratumoral injection, essentially accumulate in the liver tumor. Most of the radiotracer remained in the tumor up to 48 hr postintratumoral injection. The radioactivity level in the tumor was significantly higher than that in the normal liver tissue throughout the study. The concentration of radioactivity in the lung at 1 hr indicated that there might be some leakage of the tracer from the tumor. Leakage was also noted by Tian et al. (*11*) in their study using ^{90}Y microspheres. The activity in the kidney was higher than in the systemic organs other than the lungs, and the concentration in urine was marked. This would suggest that the excretion route for the ^{188}Re component is through the urine. In the spleen, testis, muscle and blood, the radiation activities were insignificant. For a tumor of 2 cm in diameter, 1000 MBq ^{188}Re microspheres would deliver >63,600 cGy (rad) to the tumor, while delivering only 122 cGy to the normal liver tissue (Table 3). This is well below the reported tolerance dose for external-beam irradiation of the liver (3000 cGy) (*24*). In addition, the estimated doses to other organs such as the lung, kidney and red marrow are also very low. Except for the tumor, the urinary bladder has the highest estimated dose. However, this is not a clinical limiting factor because the radiation dose to the urinary bladder is low and the urinary bladder is quite radiation resistant. In addition, the radiation dose to the red bone marrow is very low. This indicates that bone marrow suppression will also not be a clinical limiting factor.

According to our data, 60% of rats showed a significant decrease in tumor size after intratumoral injection of ^{188}Re microspheres. The tumor disappeared in three rats. In most rats, the response was obvious in the second week and lasted to the fourth week post-treatment. Interestingly, two rats (Rats 1 and 12) had significant decreases in tumor size in the second week, but the tumors rebounded in the fourth week. These findings suggest a repeated intratumoral injection of ^{188}Re microspheres is necessary in some patients between the second and fourth weeks after treatment. In the control group, the median survival time was only 17 days. In contrast, 80% of the rats survived over 60 days after ^{188}Re microsphere treatment.

Compared to our previous study using intrahepatic arterial injection of ^{188}Re-lipiodol in treating hepatoma (*10*), the current method (direct intratumoral injection of ^{188}Re microspheres) showed a higher radiation dose to the tumor and a lower radiation dose to the normal liver. However, the radiation safety of the direct intratumoral injection method, especially to the medical personnel who perform the injection, still needs to be explored further before this procedure can be applied as a standard method for the treatment of malignant hepatic tumor (*25*).

CONCLUSION

Direct intratumoral injection of ^{188}Re microspheres is a potential agent for the treatment of liver tumor. However, repeated injection may be necessary 2 wk after the first treatment.

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Carbon-11-Thymidine and FDG to Measure Therapy Response

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This study was performed to determine if PET imaging with ^{11}C-thymidine could measure tumor response to chemotherapy early after the initiation of treatment. Imaging of deoxyriboneucleic acid biosynthesis, quantitated with ^{11}C-thymidine, was compared with measurements of tumor energetics, obtained by imaging with ^{18}F-fluorodeoxyglucose (FDG). **Methods:** We imaged four patients with small cell lung cancer and two with high-grade sarcoma both before and approximately 1 wk after the start of chemotherapy. Thymidine and FDG studies were done on the same day. Tumor uptake was quantified by standardized uptake values (SUVs) for both tracers by the metabolic rate of FDG and thymidine flux constant (K_{TdR}) using regions of interest placed on the most active part of the tumor. **Results:** In the four patients with clinical response to treatment, both thymidine and FDG uptake markedly declined 1 wk after therapy. Thymidine measurements of SUV and K_{TdR} declined by 64% ± 15% and 84% ± 33%, respectively. FDG SUV and the metabolic rate of FDG declined by 51% ± 9% and 63% ± 23%, respectively. In the patient with metastatic small cell lung cancer who had disease progression, the thymidine SUV decreased by only 8% (FDG not done). In a patient with abdominal sarcoma and progressive disease, thymidine SUV was essentially unchanged (declined by 3%), whereas FDG SUV increased by 69%. **Conclusion:** Images show a decline in both cellular energetics and proliferative rate after successful chemotherapy. In the two patients with progressive disease, thymidine uptake was unchanged 1 wk after therapy. In our limited series, K_{TdR} measurements showed a complete shutdown in tumor proliferation in patients in whom FDG showed a more limited decrease in glucose metabolism.

Key Words: PET; thymidine; fluorodeoxyglucose

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PET provides a way of measuring regional tumor metabolism and the response to therapy. At present, clinicians use techniques that measure the change in size of a tumor to determine if it is responding to chemotherapy. Because tumor shrinkage is often delayed after successful cytotoxic therapy, anatomic imaging is typically repeated after at least 2 mo of therapy. Even then, persistence of fibrotic or inflammatory masses may make it difficult to judge true tumor response to treatment. PET can aid in this task, because metabolic changes in the tumor are expected to precede changes in size. As PET is being developed for tumor imaging, among the major issues to be addressed are the optimal imaging agent to be used and the timing of imaging. Fluorodeoxyglucose (FDG) has been the most widely used agent in PET tumor imaging. This stems in part from its relatively straightforward synthesis, long half-life for a PET radionuclide (110 min) and high tumor uptake. FDG may encounter problems in some situations in which tumor cells may continue to be energetically active even after their replicative machinery has been damaged. Furthermore, FDG may be taken up by inflammatory cells such as macrophages found in dying tumors (*1*). We have, therefore, sought to study tracers that may be more closely tied to cellular proliferation (*2,3*).

Because thymidine is readily taken up by cells and incorporated into deoxyriboneucleic acid (DNA), it has been used for many years to assess cell growth when labeled with long-lived tracers such as ^{14}C and ^{3}H. Studies in rats have shown that DNA and protein biosynthesis decline after therapy more promptly than FDG uptake (*4*). We have been studying ^{11}C-thymidine kinetics compared with FDG in patients undergoing chemotherapy. The ability to label thymidine with ^{11}C allows the production of images of uptake and retention (*5,6*). In patients with lymphoma, ^{11}C-thymidine uptake correlated with tumor grade (*7*). Carbon-11-thymidine can be produced for PET imaging with the label in either the methyl or ring-2 positions. The ring-2 form of thymidine was chosen because it is primarily degraded to CO_2, which simplifies its quantitation and modeling (*8,9*). In this study, we examined the changes seen in thymidine uptake early after the onset of chemotherapy in patients with small cell lung cancer and sarcoma. This study

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