for radiotherapy, because they can be labeled with any nuclide in principle and can deliver a large amount of radionuclide close to the tumor.

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Hepatic Artery Injection of Yttrium-90-Lipiodol: Biodistribution in Rats with Hepatoma

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In this study, we analyzed the biodistribution of ^{90}Y-lipiodol in rats with liver tumors (hepatoma) following hepatic arterial injection. **Methods:** Sixteen male Sprague-Dawley rats with liver tumors were killed at 1, 24, 48 and 72 hr (four rats at each time) after injection of approximately 0.1 mCi ^{90}Y-lipiodol through the hepatic artery, respectively. Samples of tumor, liver, spleen, skeletal muscle, lung, kidney, bone, whole blood and testis were obtained and counted to calculate the tissue concentrations (%ID/g). **Results:** We found that the radioactivity in the liver tumor was high at 1 and 24 hr and then declined slowly. The biological half-time was 84.1 hr. The radioactivity in normal liver tissue was also high at 1 hr but was significantly lower than that in the tumor. The biological half-time was 38.5 hr. The ratio of tissue concentration between liver tumor and normal liver tissue (T/N ratio) was 3.03 at 1 hr and rose to 6.45 at 72 hr. The radioactivity in the lung was almost as high as in normal liver tissue at 1 hr and declined rapidly with a biological half-time of 25.6 hr. The activity levels of the kidney were moderate at 1 hr and remained at almost the same level throughout the study. A moderate concentration of radioactivity in bone was noted within the first 24 hr. The concentration, however, rose over the ensuing time. The concentration of radioactivity in skeletal muscle, spleen, testis and whole blood was quite low. **Conclusion:** Following hepatic arterial injection of ^{90}Y-lipiodol, tracer uptake in liver tumor was high and tumor retention was lengthy. Consequently, large radiation doses could be delivered to the tumor. We suggest that ^{90}Y-lipiodol is a potential agent in the treatment of liver malignancy.

Key Words: lipiodol; yttrium-90; transarterial internal radiation therapy; hepatic cancer

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Lipiodol, an iodinated ester derived from poppy-seed oil, has been found to be selectively retained within hepatic tumors (*1,2*), and is widely used in the treatment of irresectable primary hepatoma when combined with anticancer drugs or labeled with ^{131}I. These preliminary results are encouraging (*3–7*). Furthermore, some investigators believe ^{90}Y to be a better radiotherapeutic candidate than ^{131}I since ^{90}Y has several advantages over ^{131}I, including a shorter half-life which is more suitable for therapy, lack of gamma-ray emissions, a longer beta energy range sufficient to kill cells, few shielding problems and little radiation exposure to surrounding normal tissues (*8,9*). Yttrium-90-microspheres have been reported to be safe and useful in the treatment of hepatocellular carcinoma (*10–12*). Recently, we successfully labeled lipiodol with ^{90}Y (*13*). In this study, we analyzed the kinetics and biodistribution of ^{90}Y-lipiodol in rats with hepatic tumors following intrahepatic arterial injection to assess its potential utility in targeted therapy.

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MATERIALS AND METHODS

Preparation of Yttrium-90-Lipiodol

Separation of Yttrium-90 from Strontium-90. An RP-18 column was used to separate ^{90}Y from ^{90}Sr as follows:

1. One milliliter lipiodol ultro-fluida (Guerbet, France) was passed through a 100-mg Adsorbex RP-18 column.
2. The column was washed with 3 ml n-hexan followed sequentially by 1 ml methylethyl ketone, ethyl alcohol, water and 0.1 N HCL.
3. The column was washed again in reverse sequence, as in step 2, to induce low polarity in the column to retain the extractant, D2EHP (di-2-ethyl hexathyl phosphate, Sigma, St. Louis, MO).
4. One milliliter D2EHP was applied to the pretreated column and allowed to drip overnight. The last drop of D2EHP was blown out by a syringe adapted to the top of the column. About 150 μl D2EHP were retained in the column.
5. An equilibrium solution of ^{90}Sr and ^{90}Y was added to the D2EHP packed column.
6. The column was washed with water until no radioactivity was detected in the elution. Only ^{90}Y was retained in the column.

Conjugation of lipiodol with N, N, N', N'-tetrakis (2-benzymidazolylmethyl)-1, 2-ethanediamine (EDTB). This process was as follows:

1. The EDTB was prepared by refluxing stoichiometric quantities of ethylenediamine-tetra-acetic acid (EDTA) and 1,2-phenylenediamine in glycol for 20 hr following precipitation with water.
2. The crude product was purified by recrystallization from hot (50°C) absolute ethanol.
3. Twenty milligrams EDTB in 1.5 ml glacial acetic acid were added to 10 ml lipiodol and incubated at 70°C for 4 hr.
4. The dissolved acetic acid was removed overnight by bubbling with argon and by a connected vacuum.
5. The EDTB conjugated lipiodol solution was obtained by filtration through a millipore 0.2 μm filter.

Yttrium-90 Labeling of Lipiodol. Lipiodol was labeled as follows:

1. One hundred microliters lipiodol were added to the ^{90}Y retained column.
2. The emulsified eluant was discarded.
3. One milliliter EDTB conjugated lipiodol was passed through the column.
4. Yttrium-90-lipiodol was collected from the eluant.
5. The final solution was diluted with lipiodol to an adequate radioactivity level and volume before use.

The radionuclide impurity of ^{90}Sr contained in the final product is less than 10^{-6}%. The labeling efficiencies were all greater than 98%, even after 48 hr at room temperature. After incubation at 37° with human serum for 4 and 24 hr, the label was still above 90% intact.

Animal and Tumor Cell Line

Male Sprague-Dawley rats weighing 200–250 g were used in this study. The rats were fed a standard chow diet and were given water ad libitum. A N1-S1 hepatoma cell line which originates from rat was used for tumor implantation. The tumor cells were routinely cultured in Dulbecco's Modified Eagle Medium (GIBCO, Paisley, U.K.) mixed with 5% fetal bovine serum, 1% L-glutamine and 20% horse serum. After growing exponentially for 1 wk, a concentration of approximately 4×10^7 cell per ml could be established. Cell viability was over 90% as determined by trypan-blue exclusion.

Inoculation

The rats were anesthetized by intraperitoneal injection of ketamine at a dose of 10 mg/100 g. Subxyphoid laparotomy, 1.5-2 cm in length, was then performed to expose the left or right lobe of the liver. A 27-gauge needle was used to slowly inject a tumor cell suspension containing 4×10^6 cells in a volume of 0.1 ml into one of the hepatic lobes under the liver capsule to raise a visible pale wheal. The puncture site was gently compressed by cotton gauze for 15 sec to prevent bleeding. The wound was closed in layers. Two weeks after inoculation, laparotomy was again performed to check tumor growth.

Intrahepatic Arterial Injection of Yttrium-90-Lipiodol

Under anesthesia by intraperitoneal injection of ketamine, midline laparotomy was performed. The hepatic artery and the gastroduodenal branch were identified and isolated. A temporary sling was placed around the hepatic artery proximal to the gastroduodenal branch to prevent back flow. After ligation of the distal end of the gastroduodenal branch, this artery was cannulated with a fine polyethylene tubing. The tubing was secured in the vessel with a fine silk tie and connected to a syringe. Following injection of 0.1 mCi ^{90}Y lipiodol in a volume of 0.1 ml, the cannula was flushed with 0.2 ml saline, removed and the proximal end of the gastroduodenal branch was ligated. The sling around the hepatic artery was removed and hepatic arterial circulation restored.

Biodistribution

Sixteen rats bearing liver tumors (Fig. 1) were used to determine tissue biodistribution of ^{90}Y-lipiodol and to understand its in vivo behavior. The rats were killed with sodium pentobarbital at 1, 24, 48 and 72 hr (four rats at each time) after injection of approximately 0.1 mCi ^{90}Y-lipiodol through the hepatic artery. Samples (about 0.1 g) of tumor, normal liver, spleen, skeletal muscle, lung, kidney, bone, testis and whole blood (0.5 ml) were taken and weighed carefully. Two milliliters of tissue solubilizer were added, after which the samples were incubated at 50° for 2–4 hr to achieve tissue lysis. Bone tissue was treated with 2 ml 10 N HCL and kept at room temperature for 18 to 24 hr. A small amount of hydrogen peroxide was added to bleach the samples. After tissue lysis was completed, 10 ml LSC-cocktail were added and the solution was mixed well. Four hours later, a liquid scintillation counter was used to measure the radioactivity. Tissue concentrations were expressed as the percent injected dose per gram.

Radiation Dose Calculation

The radiation dose to various organs was calculated using the MIRDOSE software program. The exposure dose to the tumors

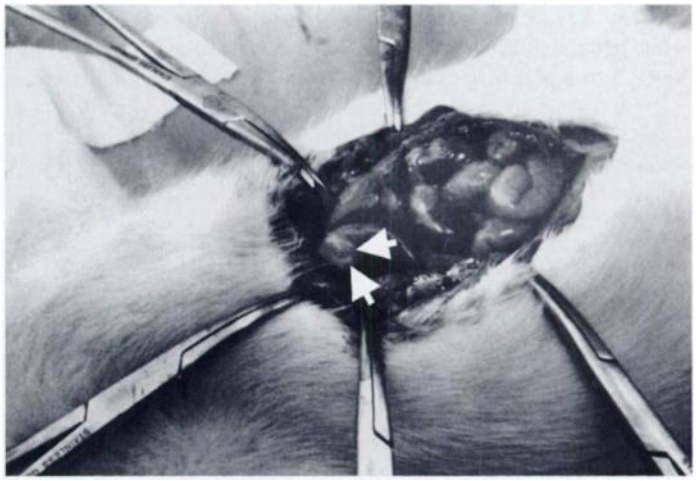

FIGURE 1. A solitary tumor (arrow) about 0.8 × 0.8 cm in size develops in the liver 2 wk after direct innoculation of N1-S1 heaptoma cell ine.

TABLE 1
Tissue Distribution of Yttrium-90-Lipiodol in Rats with Liver Tumor

Time (hr)	Tissue concentration (%ID/g)* (mean ± s.d.)								
	Tumor	Liver	Lung	Kidney	Spleen	Testis	Skeletal muscle	Bone	Blood
1	7.37 ± 1.38	2.44 ± 0.59	2.47 ± 0.30	1.15 ± 0.21	0.28 ± 0.06	0.02 ± 0.00	0.19 ± 0.03	0.37 ± 0.08	0.00 ± 0.00
24	7.33 ± 1.11	1.40 ± 0.24	1.41 ± 0.21	0.71 ± 0.10	0.11 ± 0.04	0.02 ± 0.00	0.08 ± 0.01	0.36 ± 0.06	0.00 ± 0.00
48	5.82 ± 0.98	0.94 ± 0.28	0.11 ± 0.04	1.04 ± 0.11	0.18 ± 0.04	0.02 ± 0.00	0.17 ± 0.03	0.96 ± 0.11	0.00 ± 0.00
72	4.52 ± 0.83	0.70 ± 0.08	0.06 ± 0.01	1.03 ± 0.08	0.14 ± 0.05	0.01 ± 0.00	0.10 ± 0.01	0.78 ± 0.09	0.00 ± 0.00

*Average value of four rats for each time interval.

was calculated according to the methods reported by Siegel and Stabin (*14*).

RESULTS

Biodistribution of ^{90}Y-lipiodol in various organs is shown in Table 1. Our data show that radioactivity in the liver tumor was high at 1 and 24 hr, after which it declined. The biological half-time was 84.1 hr. The radioactivity in normal liver tissue was also high at 1 hr but was significantly lower than that in the tumor. The biological half-time was 38.5 hr. The ratio of tissue concentration between liver tumor and normal liver tissue (T/N ratio), shown in Table 2, was 3.03 at 1 hr and increased to 6.45 at 72 hr. The radioactivity in the lung was almost as high as that in normal liver tissue at 1 hr but declined rapidly. The activity levels in the kidney were moderate at 1 hr and remained at almost the same level throughout the study. A moderate concentration of radioactivity in bone was observed within the first 24 hr. The concentration, however, increased over the ensuing time. The concentration of radioactivity in skeletal muscle, spleen, testis and whole blood was quite low throughout the study. The estimated doses of various organs are shown in Table 3.

DISCUSSION

Our data show that the ^{90}Y-lipiodol was primarily accumulated in the liver tumor and normal liver tissue after intrahepatic injection. The radioactivity in the tumor was significantly higher than that in the normal liver tissue. The T/N ratio was as high as 3.03 and increased progressively to 6.45 throughout the study. The reason for the selective accumulation of ^{90}Y-lipiodol in the liver tumor is not known. The vascularity of hepatic tumors may play a significant role. The greater tumor vascularity, which derives more than 90% of its blood flow from the hepatic artery whereas normal liver derives only 30%, may explain the greater tracer concentration within the tumors. In addition, the marked permeability of abnormal tumor vessels may also explain the increased uptake (*1,2,15–18*).

Lipiodol is normally catabolized by the liver and is cleared from the normal liver over a period of a few days (*19*). The retention of lipiodol in tumors, however, is reportedly much longer (*5,15,16*). The biological half-life of the ^{90}Y-lipiodol in the tumor was 84.1 hr, over twice as long as that in the normal liver (38.5 hr). It is not clear why ^{90}Y-lipiodol remains longer in the tumor than in normal liver tissue. There are several possible explanations. Kobayashi et al. (*20*) have suggested that the stagnation of lipiodol droplets in tumor vessels is due to electrostatic adsorption induced by changes in the electrical charge of the inner wall. Furthermore, the slow disappearance from the tumor may be due to the absence of lymphatic vessels and Kupffer cells in tumor tissues, the two avenues by which lipiodol is thought to be removed from normal hepatic parenchyma (*15–18,21*).

The high concentration of radioactivity in the lung at 1 hr was considered to result from arterial-portal-systemic-shunting in the liver. In vivo microscopy in rats showed that lipiodol enters the portal branches through arterial-portal shunting and also passes through the sinusoids into the hepatic veins and the general circulation after hepatic arterial injection (*22*). In the presence of liver tumor, the escape of radiotracer from the liver should be more evident, since the AV shunt is usually present in liver cancer (*23,24*). Arteriovenous shunting from the liver to the lung may be a potential adverse factor for the treatment of hepatic cancer. Therefore, in clinical practice, a scintigraphic tracer study should precede intra-arterial therapy for assessment of the correct catheter positioning and degree of AV shunting.

Radioactivity in the kidney was also initially and persistently high. This phenomenon suggests that some ^{90}Y-lipiodol passing the liver through the AV shunt was not captured by the lungs. It is well known that about 2% of the cardiac output bypasses the pulmonary capillary bed (*25*). Subsequently, radioactivity in the kidney remained at almost the same level. Lipiodol seems to be eliminated in the form of two components: an iodine component excreted through the urinary tract and a lipid component excreted through the biliary tract. Raoul et al. (*26*)

TABLE 2
Ratios of Tissue Concentration between Liver Tumor and Normal Liver Tissue

Time (hr)	T/N ratios (Tumor/Normal liver)
1	3.03 ± 0.42
24	5.25 ± 0.65
48	6.15 ± 1.01
72	6.45 ± 0.87

TABLE 3
Estimated Doses (rad) of Various Tissues in Rats from Yttrium-90-Lipiodol

Tissue	Doses (rad/mCi)
Tumor*	654.92
Liver	25.30
Lungs	2.01
Kidney	6.93
Spleen	1.20
Testes	1.78
Muscle	0.95
Red marrow	12.69
Bone surfaces	15.34
Total body	2.44

*Tumor size was assumed to be approximately 3 cm in diameter.

reported that ^{131}I-lipiodol activity was eliminated primarily through the urine (*26*). Our data also suggest that the probable excretion route, certainly for the ^{90}Y component, is through the urine. As for the spleen, testis, skeletal muscle and blood, the activity was relatively insignificant.

The radioactivity level in the bone was moderate initially but increased about twofold after 48 hr. The data indicated that some of the activity, released from the liver, accumulated in the bone instead of being excreted by the kidney. Since the bone marrow is a highly radiosensitive organ (*27–29*), the radiation burden in the skeletal system (particularly the trabecular bone) may become the most important limitation for the usage of ^{90}Y-lipiodol in the treatment of liver malignancy.

In the estimation of the tumor doses, the S-values for ^{90}Y in spheres of 1 g/cm^3 density reported by Seigel and Stabin show significant variance according to different sphere sizes (*14*). The total amount of radiotracer accumulated in the tumor must also vary according to different tumor sizes. If the tumor uptake in humans is assumed to be the same as the tumor uptake in the animal model (in fact, the total amount of radiotracer must be significantly higher in a larger tumor), clinically, for a 10-g (about 2.5–3 cm in diameter) tumor, 15 mCi ^{90}Y-lipiodol would deliver more than 9800 rad to the tumor while delivering only 380 rad to the normal liver tissue, and lower than 190 rad to the red marrow. The dose to the liver is well below the reported tolerance dose for external beam irradiation (3000 rad) (*30*). As for the red marrow, myelodepression may occur but is always mild and reversible under the dose exposure of 190 rad (*31,32*). In addition, the radiation dose to the tumor in this study was certainly underestimated. In clinical application, the therapeutic dose can decrease and the uptake of ^{90}Y-lipiodol should be higher than 7% in a larger tumor. Therefore, the radiation exposure to the red marrow must be lower. Our results suggest that ^{90}Y-lipiodol should be more effective than ^{131}I ethiodol in the treatment of hepatoma when compared with the results of Madsen et al (*8*).

CONCLUSION

Tracer uptake in liver tumor following hepatic arterial injection of ^{90}Y-lipiodol was high and the retention was long. As a result, large therapeutic radiation doses could be delivered to the tumor. After serious evaluation of the degree of AV shunts in the liver and radiation burden to the skeletal system, we believe that ^{90}Y-lipiodol may become a potential agent for the treatment of liver malignancy.

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