Optimal Radiolabeled Liposomes for Tumor Imaging

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We conducted a systematic study of the effects of liposome formulation and encapsulated radionuclides on imaging ability. **Methods:** Various types of liposomes were prepared and labeled with ^{67}Ga, ^{111}In or ^{99m}Tc. Their tumor-imaging potential was evaluated in terms of tumor accumulation and tumor-to-blood ratios of radioactivity delivered by the liposomes. Mouse sarcoma 180 and Ehrlich solid tumor were the tumor models. **Results:** Liposomes could be labeled rapidly and with high efficiency, which was sufficient for clinical application. Tumor accumulation of liposome-encapsulated radionuclides that have intrinsic tumor affinity, such as ^{67}Ga-NTA or ^{111}In-NTA, was larger than that of the other nuclides. Liposomes that were fairly small, cholesterol-rich and composed of so-called rigid phospholipids, could deliver large amounts of encapsulated radionuclides to the tumor. We also found that tumor uptake of such liposomes was large and their blood retention was prolonged. Liposomal lipid dose also influenced tumor delivery and blood retention. The results suggest that these factors extended liposomal blood retention and, consequently, increased tumor uptake of the liposomes and tumor delivery of encapsulated radionuclides. Not all liposomes with long blood retention, however, are suitable for tumor imaging. Incorporation of monosialo-ganglioside in the liposomal membrane greatly extended blood retention but increased tumor uptake only slightly and, consequently, made the tumor-to-blood value worse. One of the ^{67}Ga-labeled liposome formulations resulted in high tumor uptake and tumor-to-blood ratios in various tumor models as well as clearly visualized tumors clearly in sarcoma 180-bearing mice. **Conclusion:** For tumor imaging with radiolabeled liposomes, we should choose liposomal formulations and dose to give prolonged blood retention for large tumor delivery. We must then select liposomes that give good tumor-to-blood values. For the best results, the radionuclide should have intrinsic tumor affinity. Labeled liposomes that meet these criteria result in excellent tumor images.

Key Words: liposome; tumor imaging; gallium-67; indium-111; technetium-99m

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Liposomes, or artificial lipid vesicles, are among the most promising carriers of therapeutic agents, being biodegradable, easy to prepare and nontoxic. Their distribution and pharmacokinetics can be modified by changing their size, charge, lipid composition and so on (*1,2*). Such properties also make liposomes attractive as radiopharmaceuticals. Several attempts have been made to apply liposomes as tumor imaging agents by encapsulating gamma-emitters in them (*3–11*), and some clinical trials have already been started (*12–14*). Systematic studies to develop optimal radiolabeled liposomes for tumor imaging have not yet been conducted, even though the essential characteristics of liposomes for imaging should be different from those for drug delivery.

When therapeutic agents are encapsulated in liposomes, the main goals are to increase efficacy, decrease toxicity and increase ease of administration. On the other hand, in the application of liposomes to tumor imaging agents, the guiding factors should be tumor accumulation of radioactivity and tumor-to-normal tissue ratios. In this study, we therefore first examined various liposome formulations and encapsulated radionuclides in relation to those guiding factors. Previously, we have shown that liposomal membrane components, such as phospholipids and cholesterol, have a great influence on the tumor delivery of radionuclides encapsulated in liposomes (*8,9*). Nevertheless, other factors are also important. Therefore, we examined various factors, including those mentioned above, to find optimal conditions for tumor imaging with labeled liposomes. In addition, we discuss how such factors influence the tumor imaging potential of labeled liposomes. Furthermore, we verified the tumor imaging potential of labeled liposomes meeting the criteria in this study using various mouse tumor models. Imaging data are also presented.

MATERIALS AND METHODS

Liposome Preparation

We used the following lipids: L-α-phosphatidylcholine from frozen egg yolk (PC), L-α-dimyristoylphosphatidylcholine (DMPC), L-α-dipalmitoylphosphatidylcholine (DPPC), L-α-distearoylphosphatidylcholine (DSPC), L-α-diarachidoylphosphatidylcholine (DAPC), sphingomyelin from bovine brain (SM), cholesterol (CH) and monosialoganglioside-G_{M1} from bovine brain (G_{M1}). Small unilamellar liposomes (SUV) were prepared as previously described (*8*). For the study on the liposomal particle size, liposomes with various particle sizes were prepared by sonication for different periods and filtration through polycarbonate filters of different pore sizes (*6*). That is, liposomes with a particle size over 1 μm were sonicated for 1 min and passed through a 1.0 μm filter 10 times; liposomes of about 0.5 μm size were prepared with 5 min sonication and a 0.6-μm filter; liposomes of about 0.25 μm size, 15 min sonication and a 0.4-μm filter; liposomes of about 0.08 μm size (SUV), 60 min sonication and a 0.1-μm filter. DSPC and CH (molar ratio, 2:1) were used as liposomal lipids. The values of mean diameter of the above liposomes were estimated to be over 1 μm, 558.2 nm, 261.5 nm and 83.6 nm, respectively, by dynamic light scattering using a submicron particle analyzer (*11*). For the phospholipid component, SUV were prepared from various phospholipids and CH (2:1). For the study on CH content, DSPC-based SUV were prepared. For G_{M1} incorporation, SUV prepared from DSPC:CH:G_{M1} (1:0.5:0.1) or SM:CH:G_{M1} (1:1:0.1) were used. For the other studies, DSPC:CH (2:1) SUV were used.

Liposome Labeling

Gallium-67-Cl_3, $^{111}InCl_3$ and ^{67}Ga-citrate were used to label the liposomes. Technetium-99m-pertechnetate and hexamethylpropyleneamine oxime (HMPAO) were also used. To label liposomes with ^{67}Ga or ^{111}In, liposomes encapsulating 10 m*M* nitrilotriacetic acid (NTA) or 10 m*M* deferoxamine (DF) were labeled with each nuclide by the reported loading method (*6*). To label liposomes with ^{99m}Tc, liposomes containing 30 m*M* reduced glutathione in 10 m*M* phosphate-buffered saline, pH 6.5, were mixed with ^{99m}Tc-HMPAO by a modification of the procedure of Phillips et al. (*15*). Radioactivity localization in the liposomal aqueous phase was estimated by H_2O-octanol extraction.

Tumor Models

Sarcoma 180 (S180) or Ehrlich solid tumor (2×10^6 cells/mouse) was subcutaneously transplanted into the left hind leg of 6–7-wk-old male ddY mice. Lewis lung carcinoma (3LL) or B16

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TABLE 1
Liposome Labeling Efficiency with Gallium-67, Indium-111 and Technetium-99m and Localization of Radioactivity in Liposomal Aqueous Phase

Radionuclide	Labeling efficiency (%)	Extracted radioactivity in aqueous phase (%)
^{67}Ga-NTA	80.4 ± 8.2	98.5 ± 1.1
^{67}Ga-DF	90.1 ± 5.2	97.9 ± 2.5
^{111}In-NTA	84.4 ± 4.8	96.8 ± 3.8
^{111}In-DF	86.7 ± 6.6	98.9 ± 2.4
^{99m}Tc-HMPAO	89.4 ± 3.9	92.6 ± 3.2

Each value represents the mean ± s.d. for three experiments.

melanoma (1×10^6 cells) was transplanted into 6–7-wk-old male C57Bl/6 mice and MH134 hepatoma (5×10^5 cells) or MM46 carcinoma (1×10^6 cells) was transplanted to 6–7-wk old male C3H/He mice. When the tumor weighed between 0.1 and 0.5 g, mice were used for the following experiments.

Tissue Distribution of Radionuclides and Liposomes

Tissue distribution of radionuclides after intravenous injection of labeled liposomes was determined as described earlier (*6*). Tumor uptake of the liposomes was estimated by using cholesteryl [1-^{14}C]oleate as a marker, as described earlier (*8*). Blood clearance of liposomes was evaluated using high-performance liquid chromatography (HPLC) with a gel permeation column (*9*). The amount of intact liposomes in serum samples was determined by monitoring ^{67}Ga radioactivity retained in the liposome fraction. Results were converted to the percent administered dose in total blood by using a mouse hematocrit value of 41.5% (*16*) and total blood volume of 7.3% of the body weight (*17*).

Imaging Studies

Gallium-67-labeled liposomes (0.3 μmole as phospholipid and 1.85 MBq/0.2 ml) or ^{67}Ga-citrate (1.85 MBq/0.2 ml) were injected intravenously into sarcoma 180-bearing mice. Mice were anesthetized by intraperitoneal injection of pentobarbital before each acquisition sequence. Images were acquired at 1, 6 and 24 hr postinjection with a gamma camera equipped with a medium-energy collimator by selecting a 20% energy window centered over the 93-keV photo peak of ^{67}Ga. Data were analyzed using a MICAS-2000 computer (Aloka, Tokyo, Japan).

RESULTS

Labeling Efficiency of Liposomes with Gallium-67, Indium-111 and Technetium-99m

Liposomes were labeled with ^{67}Ga, ^{111}In or ^{99m}Tc with high efficiency (80%–90%) in every case (Table 1). The labeling procedure was completed within 30 min with any nuclides (data not shown). The water-octanol extraction showed that the radioactivity was mostly located in the liposomal aqueous phase (Table 1).

Tumor Accumulation of Liposome-Encapsulated Radionuclides

Figure 1 shows the tumor accumulation of radionuclides 24 hr after intravenous injection of liposomes encapsulating various radionuclides. The results for nonencapsulated radionuclides are also shown. Sarcoma 180 (S180)-bearing mice were used as a tumor model. Encapsulation resulted in efficient tumor uptake of nuclides, but tumor accumulation levels differed, although the nuclides were all encapsulated in the same type of liposomes. When ^{67}Ga-NTA or ^{111}In-NTA, each of which shows intrinsic affinity to the tumor even in nonencapsulated form, was encapsulated in liposomes, tumor uptake was no less than 17.3%–18.5% administered dose/g (%AD/g). When ^{67}Ga-DF, ^{111}In-DF or ^{99m}Tc-HMPAO, each of which has scarcely any tumor affinity, was encapsulated, the tumor uptake was 7.0%–8.4% AD/g. Under the same experimental conditions, tumor uptake of ^{67}Ga-citrate, which is clinically used as a tumor imaging agent, was 4.5% AD/g, and similar levels were obtained with nonencapsulated ^{67}Ga-NTA or ^{111}In-NTA.

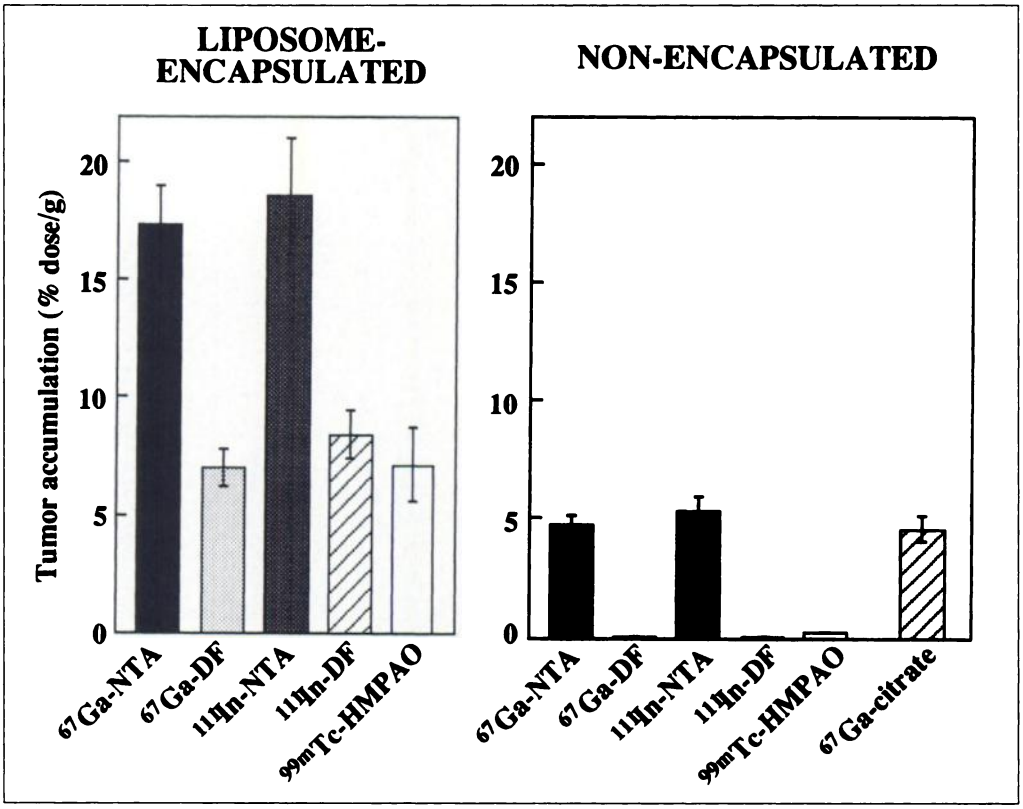

FIGURE 1. Tumor accumulation of ^{67}Ga, ^{111}In and ^{99m}Tc in sarcoma 180-bearing mice at 24 hr postadministration of liposome-encapsulated or nonencapsulated radionuclide-ligand complexes. Small unilamellar liposomes were prepared from DSPC and CH (molar ratio, 2:1). Bars indicate the mean ± s.d. for five animals.

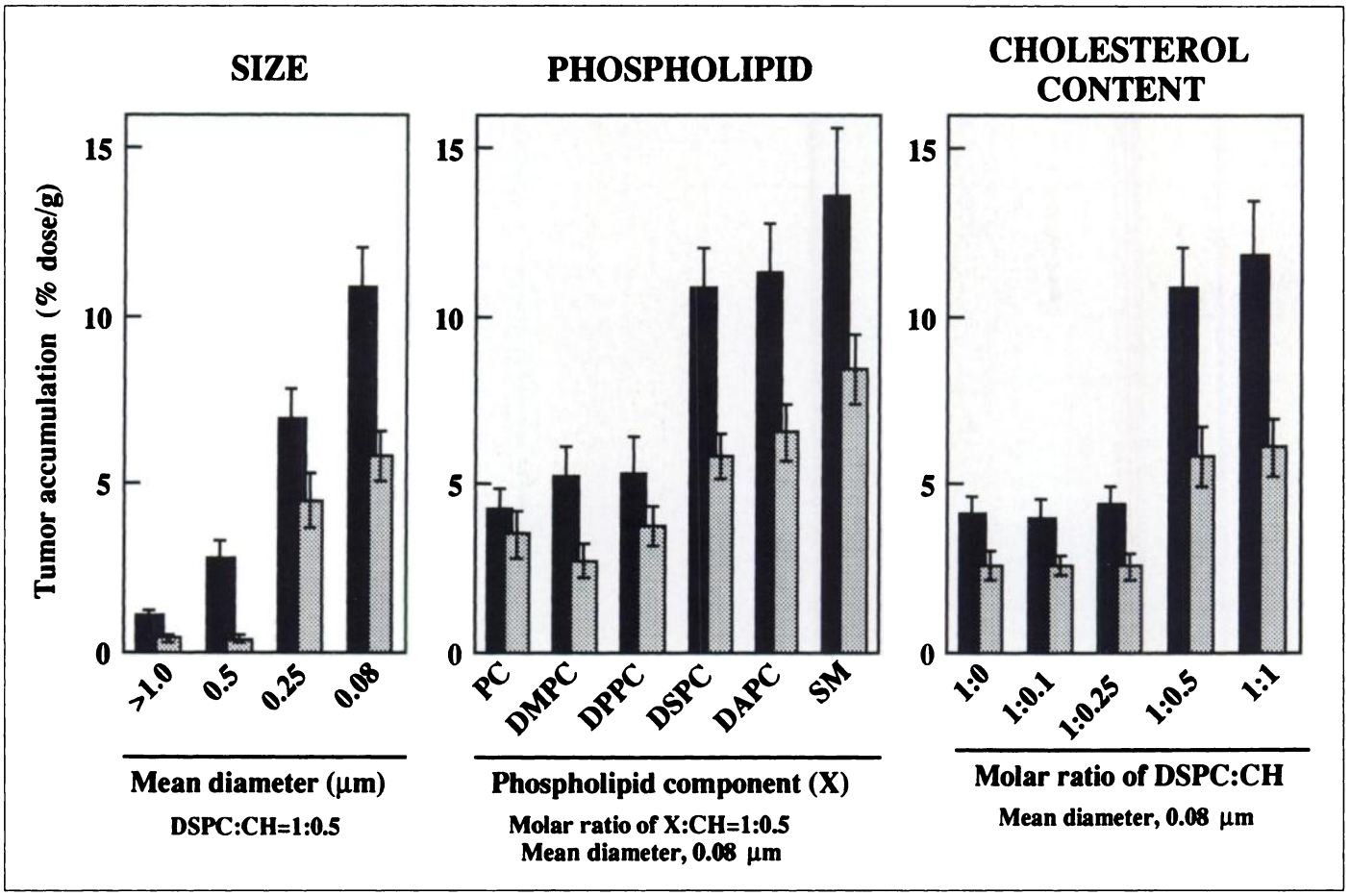

FIGURE 2. Tumor uptake of liposomes themselves and radionuclide delivery to the tumor by various types of liposomes. Liposomes were prepared as described in Materials and Methods. They were labeled with cholesteryl [1-^{14}C]oleate in the lipid phase to evaluate tumor uptake of the liposomes (▨), and ^{67}Ga-NTA was encapsulated in the aqueous phase (■). Ehrlich solid tumor-bearing mice were used as a tumor model. Bars indicate the mean ± s.d. for five animals.

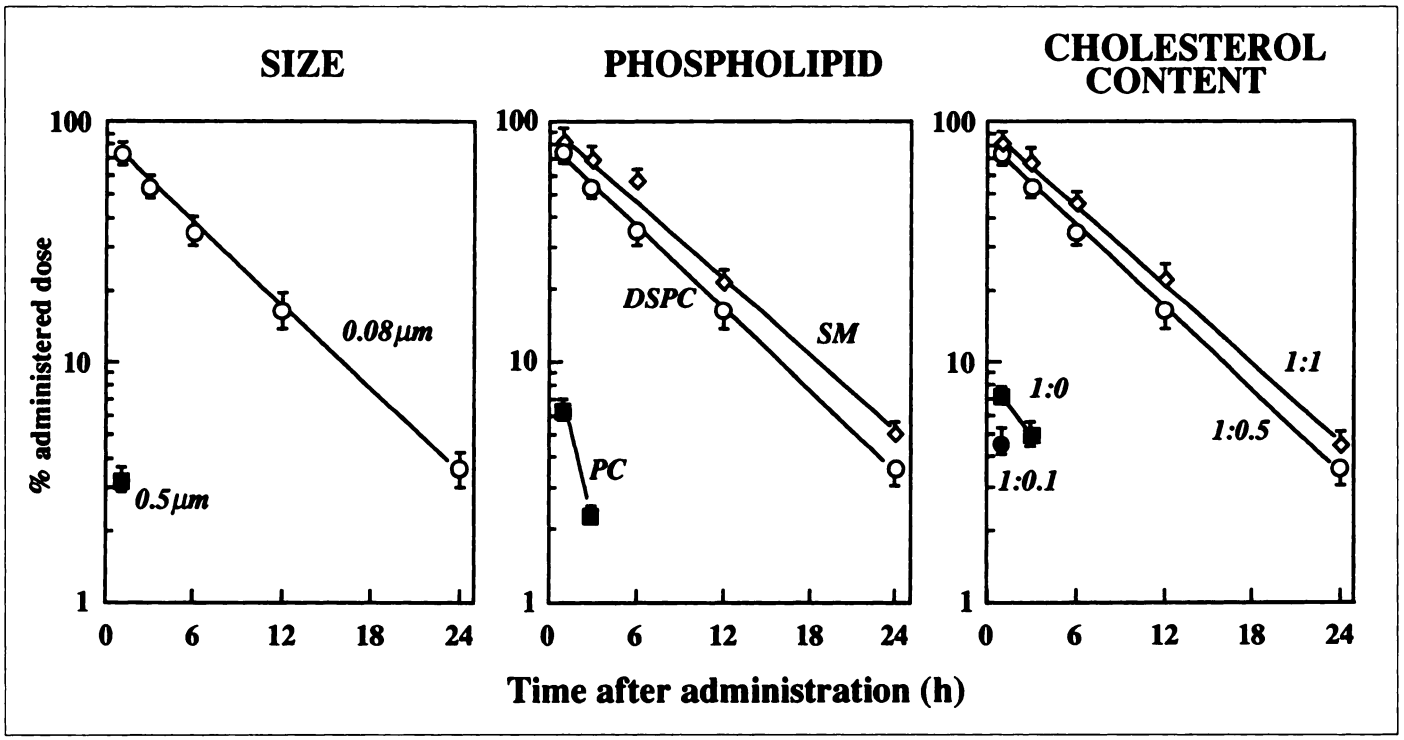

FIGURE 3. Blood clearance of various liposomes in mice bearing Ehrlich solid tumor. Symbols are the same as in Figure 2. Points indicate the mean ± s.d. for four to five animals. If data points are not shown for later time points, the liposomes were no longer detectable at those times.

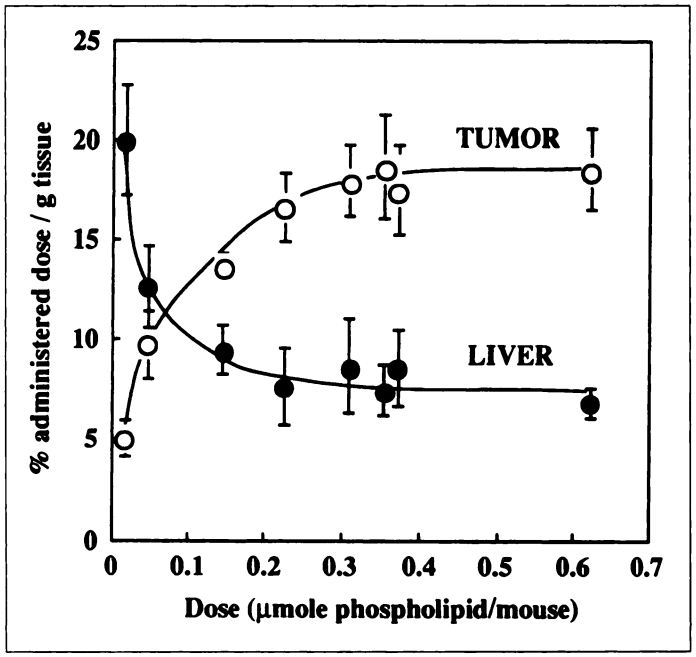

FIGURE 4. Effects of liposomal lipid dose on radionuclide delivery to the tumor by liposomes. DSPC:CH (molar ratio, 2:1)-small unilamellar liposomes encapsulating ^{67}Ga-NTA were injected intravenously into S180-bearing mice at various lipid doses and ^{67}Ga accumulations in tumor and liver were observed at 24 hr postadministration. Points indicate the mean ± s.d. for five animals.

Tumor Uptake of Liposomes and Radionuclide Delivery to Tumor

Tumor uptake of the liposomes themselves and radionuclide delivery potential were compared among various liposomes differing in particle size, phospholipid components and cholesterol content (Fig. 2). Each liposome was labeled with cholesteryl [1-^{14}C]oleate in its lipid phase to evaluate liposomal tumor uptake and ^{67}Ga-NTA was encapsulated in the aqueous phase. Ehrlich solid tumor-bearing mice were used as a tumor model. All three factors (particle size, phospholipid components and cholesterol content) greatly influenced liposomal tumor uptake and ^{67}Ga tumor delivery. We found that liposomes that were fairly small (0.08 μm in diameter), CH-rich (molar ratio of DSPC:CH; 1:0.5 or 1:1) and composed of so-called rigid phospholipids (DSPC, DAPC and SM) having high-temperature phase-transition acyl moieties, were taken up by the tumor in large quantities (5.8%–8.4% AD/g) and could deliver large amounts of ^{67}Ga to the tumor (10.9–13.6 %AD/g). Similar results were obtained when S180-bearing mice were the tumor model (data not shown).

Blood Clearance of Liposomes

Figure 3 shows the blood clearance of various liposomes in Ehrlich solid tumor-bearing ddY mice. The amount of intact liposomes existing in serum was determined with HPLC analysis by monitoring ^{67}Ga activity in the liposome fraction. It became apparent that small, rigid, CH-rich liposomes all remained in the blood circulation for a much longer time than the other liposomes.

Effects of Liposomal Lipid Dose on Radionuclide Delivery to Tumor

The DSPC:CH-liposomes (molar ratio, 2:1) encapsulating ^{67}Ga-NTA were administered to S180-bearing mice at various lipid doses. As shown in Figure 4, the ^{67}Ga tumor uptake ratio increased and finally plateaued with an increase in lipid dose. Concurrently, the liver uptake ratio decreased and plateaued. Increased blood retention was also observed with an increased lipid dose (data not shown).

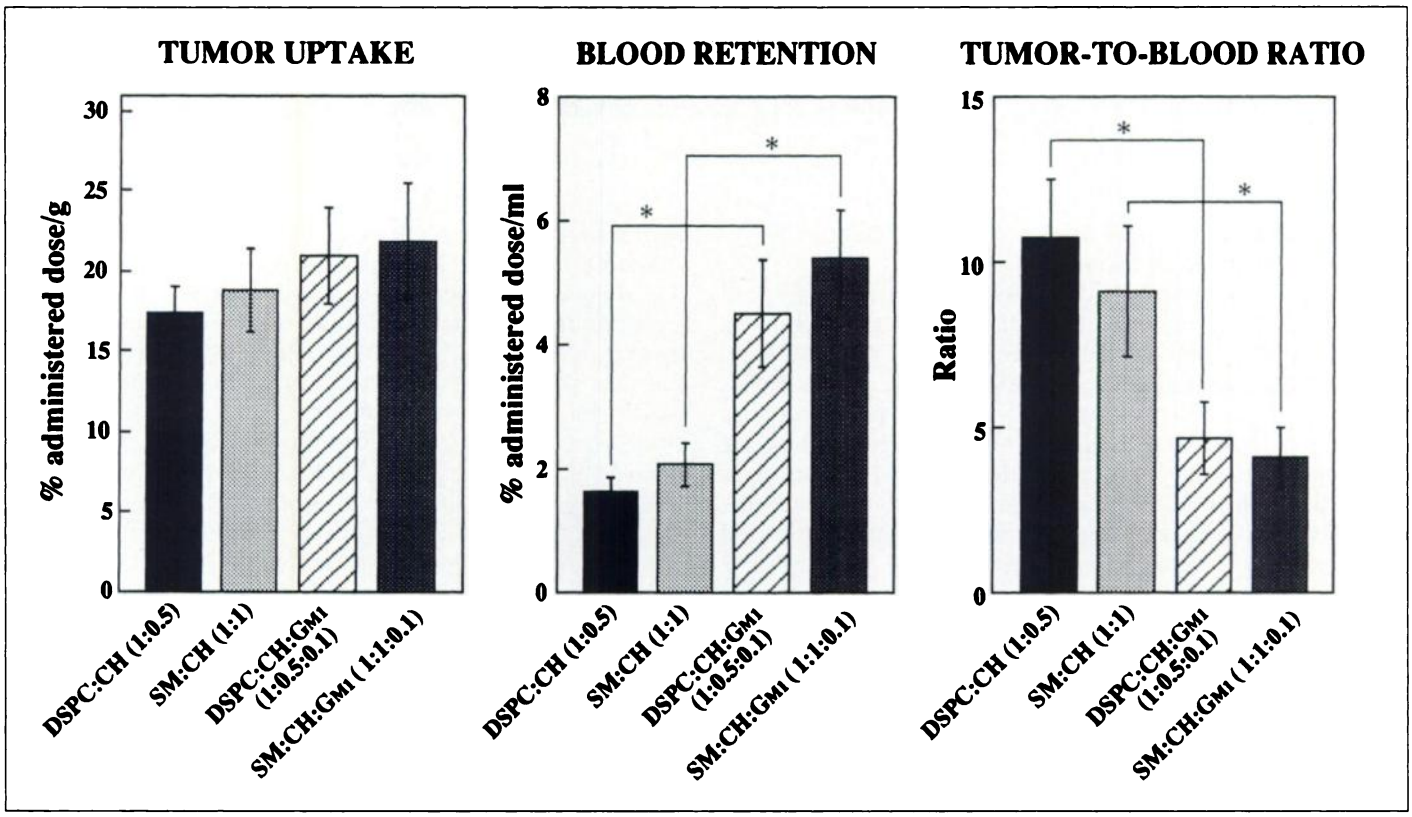

FIGURE 5. Tumor uptake and tumor-to-blood ratio of ^{67}Ga delivered by G_{M1}-modified small unilamellar liposomes. DSPC:CH:G_{M1} (1:0.5:0.1)-liposomes or SM:CH:G_{M1} (1:1:0.1)-liposomes encapsulating ^{67}Ga-NTA were administered to S180-bearing mice, and tumor uptake and blood retention of ^{67}Ga was observed at 24 hr postadministration. As a control, liposomes not containing G_{M1} were also administered in the same way. *Significantly different at $p < 0.01$. Bars indicate the mean ± s.d. for five animals.

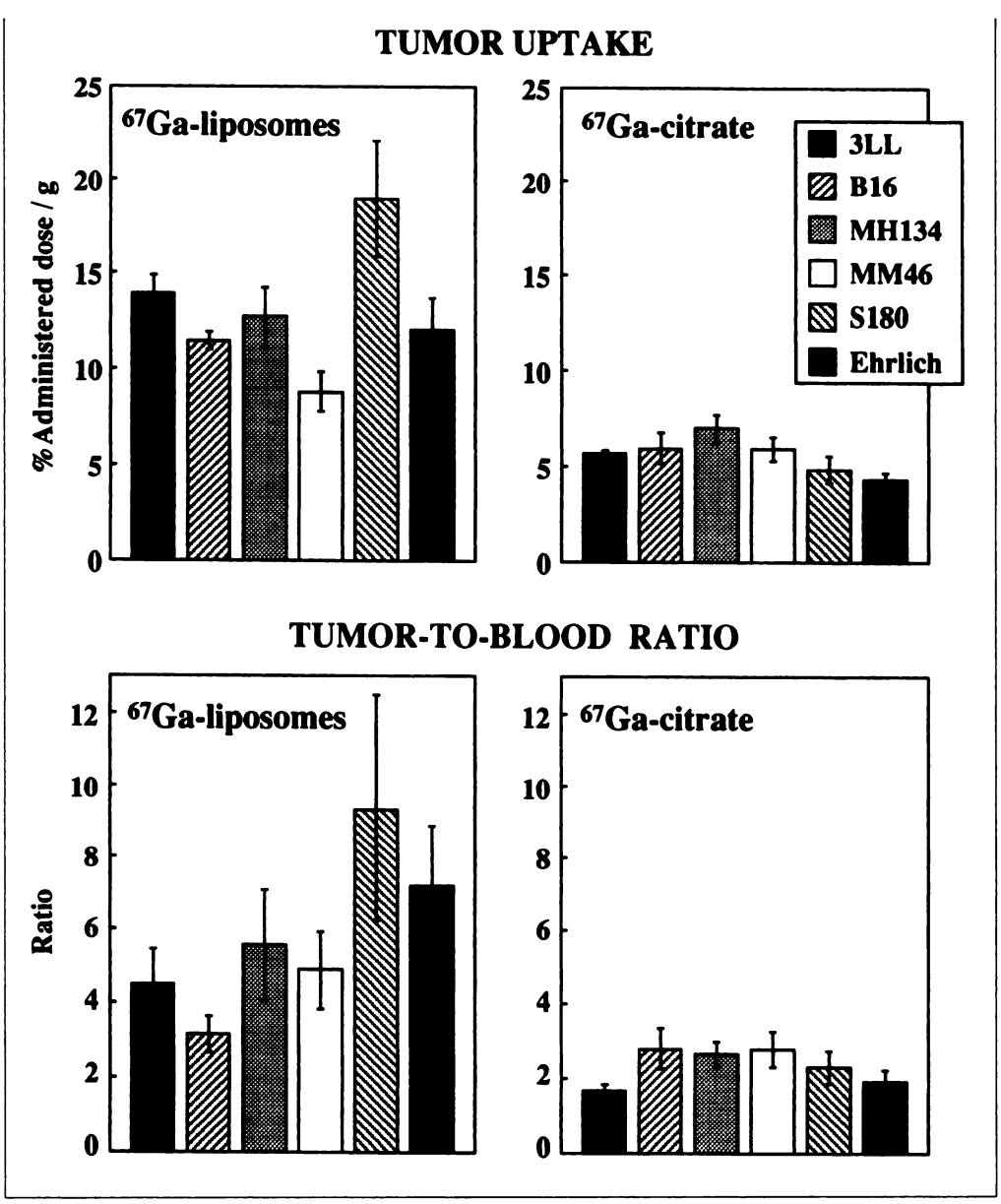

FIGURE 6. Tumor uptake and tumor-to-blood ratio of ^{67}Ga delivered by liposomes in various tumor models. DSPC:CH (2:1)-small unilamellar liposomes encapsulating ^{67}Ga-NTA were administered to mice bearing various tumors and the tumor uptake and tumor-to-blood ratio were observed at 24 hr after administration. Gallium-67-citrate was also administered similarly. Bars indicate the mean ± s.d. for five to six animals.

Tumor Uptake and Tumor-to-Blood Ratio of Gallium-67 from G_{M1}-Modified Liposomes

Monosialo-ganglioside (G_{M1}) was incorporated in liposomal membranes. DSPC:CH:G_{M1} (1:0.5:0.1) liposomes or SM:CH:G_{M1} (1:1:0.1) liposomes encapsulating ^{67}Ga-NTA were administered to S180-bearing mice. The effect of G_{M1} on ^{67}Ga tumor uptake and blood retention was observed 24 hr postadministration (Fig. 5). Incorporation of G_{M1} resulted in greatly increased blood retention compared with control liposome compositions but with only a slight increase in tumor uptake. Consequently, G_{M1} incorporation resulted in a decrease of the tumor-to-blood ratio under this experimental condition.

Tumor Uptake and Tumor-to-Blood Ratios of Gallium-67 from Liposomes in Various Tumor Models

The DSPC:CH (2:1) liposomes encapsulating ^{67}Ga-NTA were administered to various tumor-bearing mice. Tumor uptake and the tumor-to-blood ratio at 24 hr postadministration are shown in Fig. 6, which also includes the results with ^{67}Ga-citrate. In every tumor model, high tumor uptake and excellent tumor-to-blood ratios were obtained: the values were 1.5–4 times higher than those with ^{67}Ga-citrate in the same tumor model.

Tumor Imaging with Gallium-67-Liposomes

The DSPC:CH (2:1) liposomes encapsulating ^{67}Ga-NTA (0.3 μmole as phospholipid and 1.85 MBq/0.2 ml/mouse) or ^{67}Ga-citrate (1.85 MBq/0.2 ml/mouse) were administered intravenously to S-180-bearing mice, and whole-body images were obtained at 1, 6 and 24 hr postadministration (Fig. 7). When ^{67}Ga-labeled liposomes were administered, the tumor was already clearly visualized at 6 hr postadministration. At this time point, the heart was still visualized and reflected the high blood level. At 24 hr postadministration, the blood background was almost eliminated and the tumor was visualized with maximum clarity. Under the same conditions, ^{67}Ga-citrate could not detect the tumor site within 24 hr after administration.

DISCUSSION

To obtain optimal radiolabeled liposomes for tumor imaging, both the liposome-encapsulated radionuclide and the liposome formulation should be considered.

We compared three nuclides: ^{67}Ga, ^{111}In and ^{99m}Tc, each of which is suitable for gamma scintigraphy. The indices used for the comparison were the labeling efficiency and tumor accumulation level of radioactivity. For clinical application, rapid and efficient labeling is desirable, and the liposomal aqueous

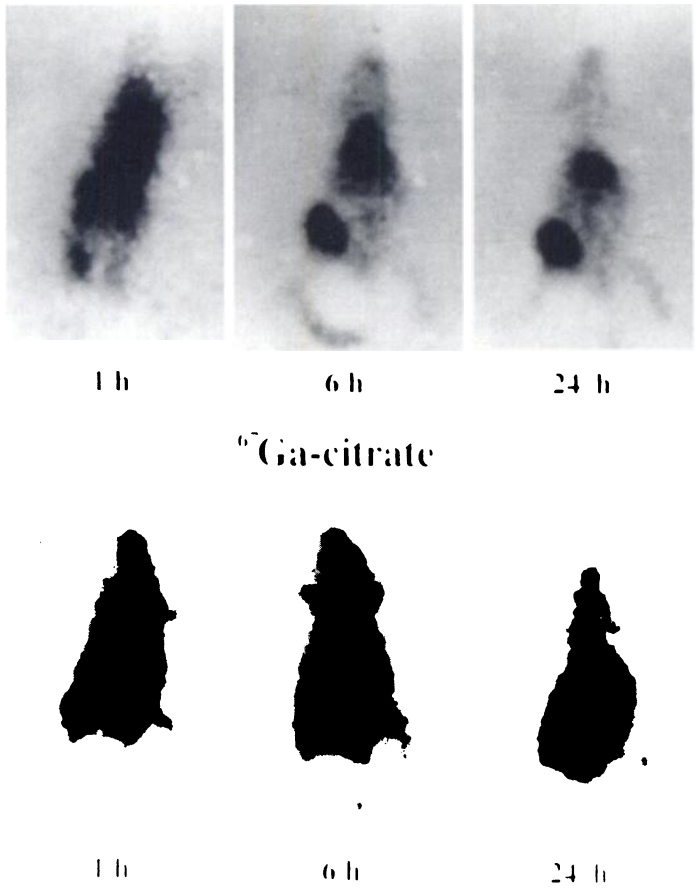

FIGURE 7. Tumor imaging by ^{67}Ga-labeled liposomes. DSPC:CH (2:1) small unilamellar liposomes encapsulating ^{67}Ga-NTA (0.3 μmole as phospholipid and 1.85 MBq/0.2 ml/mouse) or ^{67}Ga-citrate (1.85 MBq/0.2 ml/mouse) were administered intravenously to S180-bearing mice, and whole-body images were obtained at 1, 6 and 24 hr postadministration.

phase is the preferred labeling site. Liposomes can be also labeled in their lipid phase, but an aqueous label will be excreted more easily and rapidly, thereby reducing radiation exposure to the patient. We believe the labeling procedures we used in this study satisfy these requirements (Table 1) and all three nuclides were acceptable in this respect.

There were, however, some differences among the nuclides in the tumor accumulation delivered by liposomes (Fig. 1). For example, ^{67}Ga-NTA and ^{111}In-NTA gave superior results. We have already confirmed that the liposomes have high tumor affinity, but if the encapsulated radionuclide has intrinsic tumor affinity, it will tend to be retained in the tumor after being released from the liposomes. Therefore, tumor accumulation of such a radionuclide would be larger than that of the liposomes (*10*). In this study, ^{67}Ga-NTA and ^{111}In-NTA come into this category; the larger tumor accumulation of ^{67}Ga radioactivity than that of liposomes can be seen in Figure 2. The nuclides' half-lives (^{67}Ga, 78 hr; ^{111}In, 68 hr) are appropriate for tumor imaging after liposomal delivery since this takes 24–48 hr in both rodents and humans (*12*) (Fig. 7). Technetium-99m liposomes also gave acceptable results because the tumor accumulation was larger than that of ^{67}Ga-citrate. Recently, we developed a rapid tumor imaging technique using labeled liposomes (*11*), in which an image can be obtained in only 2 hr. In such a system, ^{99m}Tc-labeled liposomes would be advantageous because of its energy, half-life and cost.

We then studied the optimal conditions of liposomes for tumor imaging. The first index was tumor accumulation of radioactivity delivered by the liposomes. Our results indicated that suitable liposomes should be fairly small in particle size, composed of rigid phospholipids and be CH-rich in their formulation (Fig. 2). The liposomal lipid dose was also found to be a major factor influencing tumor accumulation (Fig. 4). We also found that the above physical properties of liposomes increased the tumor uptake of the liposomes (Fig. 2) and extended the blood retention (Fig. 3). We believe that the liposomes with long half-lives in the circulation have a greater opportunity to come into contact with the tumor and to be taken up by it, which results in greater accumulation of radionuclides in the tumor. We previously observed that small, rigid and CH-rich liposomes were fairly stable in serum and their uptake by the reticuloendothelial system (RES) was much lower than that of other liposomes (*8,9*). Presumably, the prolonged blood retention described above is the net effect of stabilization in the serum and the reduction of RES uptake. The effect of dose can probably be attributed to temporary saturation of the RES uptake, which prolongs the blood circulation at high lipid doses.

The question arises, are liposomes with longer blood retention better for tumor imaging? The results shown in Figure 5 indicate that this is not necessarily so. Recently, liposomes exhibiting greatly prolonged blood retention were developed, by incorporating certain lipids, such as monosialo-ganglioside (G_{M1}) or synthetic lipids derivatized with the hydrophilic polymer polyethylene glycol, into the liposomal membrane (*1*). Improved tumor localization was observed using such long-circulating liposomes (*18*). In tumor imaging, however, the extended blood retention would be an obstacle, causing a high blood background. This can be evaluated by using the tumor-to-blood ratio as an index. Under the experimental conditions used in this study, ^{67}Ga tumor delivery was enhanced by G_{M1}-containing liposomes, but the tumor-to-blood ratio was inferior to the control (Fig. 5). For tumor imaging, attainment of a high tumor-to-blood ratio at an early time after administration is as important as high tumor accumulation. Therefore, an appropriate balance of tumor uptake and blood level is required. Long-circulating liposomes may still be attractive candidates for tumor imaging because of their high tumor accumulation (*19*), but further investigation is needed.

CONCLUSION

Suitable liposomal formulation and dose to give prolonged blood retention are necessary to ensure high tumor uptake of liposomes and a large tumor delivery of encapsulated radionuclide. The liposomes must also give good tumor-to-blood values as early as possible. In addition, encapsulation of radionuclides that have an intrinsic tumor affinity will lead to a larger tumor accumulation of nuclides than the liposomes. The DSPC:CH (2:1) liposomes encapsulating ^{67}Ga-NTA meet these criteria. They had high tumor uptake and tumor-to-blood values in various tumor models (Fig. 6) and tumors in S180-bearing mice (Fig. 7) were clearly visualized. Liposomes that have been used for tumor imaging in clinical studies (*12–14*) also meet these criteria.

There are two applications for labeled liposomes for tumor imaging: detection of a wide variety of tumors in primary and metastatic sites and to image a specific tumor, for example, by incorporating antibodies to the corresponding tumor. Radiolabeled liposomes should be a much better tumor-imaging agent than ^{67}Ga-citrate, because their tumor uptake and tumor-to-blood ratio are larger (Fig. 6), and they can discriminate between a tumor and an inflammatory lesion (*7*). Antibody-bearing liposomes could also be useful

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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