Thierry de Baere, MD • Xiaowei Zhang, MD • Bernard Aubert, PhD • Gerard Harry, MD
Christine Lagrange, MD • Jacques Ropers, PharmD • Jacques Dufaux, PhD
Jean Lumbroso, MD • Philippe Rougier, MD • Michel Ducreux, MD • Alain Roche, MD

Quantification of Tumor Uptake of Iodized Oils and Emulsions of Iodized Oils: Experimental Study[1]

PURPOSE: **To optimize use of iodized oil for diagnostic computed tomography (CT) enhanced with iodized oil and for interstitial radiation therapy with iodine-131–labeled iodized oil, the authors quantified the distribution of iodized oil after injection of different formulations of iodized oil into the hepatic artery.**

MATERIALS AND METHODS: **I-125–labeled iodinated ethyl ester of poppyseed oil in two viscosities (iodized oil ultrafluid [viscosity, 0.04 Pa/sec] and iodized oil fluid [viscosity, 0.17 Pa/sec]) was injected (pure forms and three different emulsions of each) into the hepatic artery of rabbits bearing VX2 tumors in the liver. All rabbits received a radiation dose of 4 MBq per kilogram of body weight in 0.1 mL/kg iodized oil. Animals were killed 4 days later, and iodized oil uptake was evaluated in the tumor, nontumorous liver, and lung.**

RESULTS: **There were no statistically significant differences in uptake between pure iodized oil ultrafluid or fluid or between the same type of emulsions made with each type of iodized oil. Lung uptake was significantly higher with pure iodized oil ultrafluid and fluid (19.75 kBq/g ± 3.25 [standard error of the mean] vs 19.48 kBq/g ± 6.15, respectively) than with any emulsions (range, 3.72–8.14 kBq/g; mean, 5.68 kBq/g) except the small-droplet oil-in-water emulsion (10.51 kBq/g ± 1.18). The ratio of tumor to nontumorous liver uptake of iodized oil was significantly higher with large-droplet water-in-oil emulsions made of iodized oil ultrafluid or fluid (10.26 ± 2.88 and 9.53 ± 0.64, respectively) than with any other product (range, 4.07–5.38; mean, 4.49).**

CONCLUSION: **Use of large-droplet water-in-oil emulsions limited lung uptake and increased tumor uptake of iodized oil after intraarterial hepatic injection in rabbits bearing VX2 tumors in the liver.**

IODINATED ethyl ester of poppyseed oil (Lipiodol Ultra-Fluide; Andre Guerbet, Aulnay-sous-Bois, France) was first injected into the hepatic arteries in the early 1980s. Because of its capacity to target and remain fixed in tumors, iodized oil ultrafluid was first used as a diagnostic tool (1,2) and is still used in association with computed tomography (CT) enhanced with iodized oil for the evaluation of disseminated hepatocellular carcinoma. Hepatic artery injection of iodized oil mixed with various drugs is widely used for the treatment of liver tumors and has been frequently described in the literature during the past decade (3–6). More recently, iodinated-131–labeled iodized oil (Lipiocis; CIS Bio International Laboratories, Gif sur Yvette, France) has been injected into the hepatic artery for interstitial radiation therapy. Some clinical success has been reported with this method, notably in the treatment of hepatocellular carcinoma with portal vein thrombosis (7).

Increased tumor uptake of I-131 iodized oil improves the effects of treatment, since greater tumor uptake signifies an increase in the dose delivered to the tumor. Likewise, when CT enhanced with iodized oil is performed, greater tumor uptake will optimize the detection of tumor nodules. Thus, it is important to increase uptake of iodized oil by tumors for both diagnostic and therapeutic purposes.

The aim of this study was to quantify tumor uptake of the two pure types of iodized oil (ultrafluid and fluid) and of their emulsions.

MATERIALS AND METHODS

Animal Tumor Model

Female New Zealand rabbits weighing 2.5–3.0 kg were used (Elevage Scientifique des Dombes, Romans, France). The rabbits were maintained under standard conditions on a laboratory diet and water ad libidum. All experiments were conducted in accordance with the European Council directives and French legislation concerning animal welfare. The VX2 tumor, a human papilloma virus–induced carcinoma, was maintained by means of serial passages in the liver of carrier rabbits in our institution.

The rabbits were tranquilized with an intramuscular injection of 1 mg of acepromazine maleate (Calmivet; Vétoqinol, Lure, France) per kilogram of body weight and received a general intravenous anesthetic that contained a mixture of ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride 2% (0.1 mL/kg). The abdominal cavity was opened through a small subxyphoid midline incision. The right lobe of the liver was gently exteriorized and a small superficial incision was made at a 30° angle to the liver surface. A small piece of solidified gelatin sponge was inserted into the incision. Approximately 2–5 minutes later, when bleeding had ceased, the gelatin sponge was removed. A 2-mm^3 tumor fragment, previously maintained in NCTC 109 medium,

Index terms: Contrast media, fatty acid, 761.1266, 761.1269 • Hepatic arteries, therapeutic blockade, 761.1266 • Liver neoplasms, chemotherapeutic infusion, 761.1266

Radiology 1996; 201:731–735

[1] From the Departments of Interventional Radiology (T.d.B., X.Z., G.H., C.L., A.R.), Radiophysics (B.A., J.L.), Nuclear Medicine (J.R.), and Medicine (P.R., M.D.), Institut Gustave Roussy, 94805 Villejuif Cedex, France; and the Laboratory of Biorheology and Physicochemical Hydrodynamics, University of Paris, France (J.D.). Received March 18, 1996; revision requested April 19; revision received May 23; accepted May 28. Supported in part by a clinical research grant from the French Council of Teachers in Radiology and by grant 95-15 from the Institut Gustave Roussy. **Address reprint requests to** T.d.B.

was then placed in the opening. Once the tumor was confirmed to be completely buried in the liver parenchyma, the liver lobe was returned to the peritoneal cavity and the abdominal incision was sutured.

Iodized Oil and Emulsions

Iodized oil ultrafluid is an ethyl ester of poppyseed oil with a viscosity of 0.04 Pa/sec. Iodized oil fluid is more viscous than iodized oil ultrafluid because it is composed of 40% of an ethyl ester mixed with 60% of a glyceric ester of poppyseed oil and has a viscosity of 0.17 Pa/sec. Both pure types of I-125–labeled iodized oil were injected separately into the hepatic arteries of four animals. Six different emulsions composed of I-125–labeled iodized oil and blue patent V dye (Guerbet) were tested in three animals each. Blue patent V was used (2 mL diluted in 100 mL of saline solution) because it is routinely injected intraarterially and because its color, which is very different from that of iodized oil, facilitates analysis of the size and direction of the emulsion at light microscopy. Three oil-in-water and three water-in-oil emulsions were prepared (Table 1). Oil-in-water emulsions were composed of a discontinuous phase (internal phase) of iodized oil droplets dispersed in a continuous phase (external phase) of an aqueous solution of blue patent V. Water-in-oil emulsions were the inverse emulsions, composed of droplets of blue patent V in a continuous phase of iodized oil. Emulsions of iodized oil ultrafluid were prepared with either large or small droplets, but emulsions of iodized oil fluid could be prepared with only large droplets, owing to poor reproducibility of small-droplet emulsions prepared with iodized oil fluid. The small-droplet emulsions with internal-phase droplet diameters of 10–40 μm (> 70% with diameters of 20–30 μm) were prepared (Polytron 300; Kinematica, Littau, Switzerland) at a speed of 8,000 rpm for 10 minutes. The large-droplet emulsions with internal-phase droplet diameters of 30–120 μm (> 70% with diameters of 70–100 μm) were prepared with the pumping method (20 pushes and pulls through a stopcock between two 10-mL syringes). After the emulsions were prepared, their directions and granulometries were evaluated at light microscopy immediately before each injection.

A constant dose of iodized oil (0.1 mL/kg) and a constant dose of radioactivity (4 MBq/kg) were injected into the hepatic artery of each animal. The volume of the continuous phase of each emulsion was slightly greater than that of the discontinuous phase to facilitate preparation of the emulsion for the direction selected. Therefore, 1.8 mL/kg of water-in-oil emulsion (1 mL/kg of iodized oil + 0.8 mL/kg of blue patent V solution), or 2.20 mL/kg of oil-in-water emulsion (1 mL/kg of iodized oil + 1.20 mL of blue patent V solution), or 1 mL/kg of pure iodized oil were injected into each animal. Emulsions were obtained by gradually adding the discontinuous phase to the continuous phase when mixing.

Table 1
Characteristics of Eight Products Tested

Emulsion	Phase		Droplet Diameter (μm)
	Continuous	Discontinuous	
Iodized oil ultrafluid			
Pure*	Pure	None	0
Small droplet			
Water-in-oil†	Pure	Blue patent V	10–40
Oil-in-water‡	Blue patent V	Pure	10–40
Large droplet			
Water-in-oil§	Pure	Blue patent V	30–120
Oil-in-water‖	Blue patent V	Pure	30–120
Iodized oil fluid			
Pure#	Pure	None	0
Large droplet			
Water-in-oil**	Pure	Blue patent V	30–120
Oil-in-water††	Blue patent V	Pure	30–120

* Microscopic appearance: only iodized oil ultrafluid.
† Microscopic appearance: small droplets of blue patent V in a sea of iodized oil ultrafluid.
‡ Microscopic appearance: small droplets of iodized oil ultrafluid in a sea of blue patent V.
§ Microscopic appearance: large droplets of blue patent V in a sea of iodized oil ultrafluid.
‖ Microscopic appearance: large droplets of iodized oil ultrafluid in a sea of blue patent V.
Microscopic appearance: only iodized oil fluid.
** Microscopic appearance: large droplets of blue patent V in a sea of iodized oil fluid.
†† Microscopic appearance: large droplets of iodized oil fluid in a sea of blue patent V.

Catheterization

Two weeks after tumor implantation, 29 rabbits were tranquilized and anesthetized. Then a 2.5-F catheter (Tracker; Guerbet Biomedical, Louvres, France) was coaxially inserted through an 18-gauge needle catheter into one of the femoral arteries. The distal tip of the catheter was placed in the hepatic artery with fluoroscopic guidance to a point beyond the origin of the gastroduodenal and right gastric artery. Contrast medium was injected through the catheter to ensure correct perfusion of the liver. Intrahepatic artery infusions of pure iodized oil fluid and ultrafluid and of the six emulsions were injected manually with fluoroscopic guidance, and care was taken to avoid reflux into a gastric artery.

Radiation Quantification

All rabbits were killed with an overdose of pentobarbital injected 4 days after the hepatic artery injection. Tumors were removed for gross examination, and three samples each of the tumor, nontumorous liver, and lung were selected. These samples were each weighed and placed in a separate vial to which a 10% formaline solution was added to obtain a final volume of 1 mL. The contents of the vials were counted in a gamma counter (1282 Compugamma; Wallac OY, Turku, Finland) and corrected for physical decay, to obtain results in kilobecquerel per gram of tissue.

Statistical Analysis

The radiation counts obtained in each experimental group were analyzed and are presented as mean ± the standard error of the mean. A mixed linear model was used to assess the effects of the different types of emulsions on the uptake of iodized oil in the lung and the tumor and to determine the tumor-to–nontumorous liver uptake ratio. A random effect for the factor rabbit was included to account for the correlation that arose from repeated measurements in the same rabbit, which led to the following model: $Y_{ij} = \mu + \alpha_i + \beta_j + \epsilon_{ij}$, where Y_{ij} is a measurement made in rabbit i with the emulsion j; μ is the overall mean; α_i are the parameters that represent emulsions; β_j are random variables that represent rabbits, which are assumed to follow a normal distribution $N(0, \sigma^2_r)$; and ϵ_{ij} denotes an error term following a gaussian distribution. Comparisons among groups of emulsions were performed by comparing to zero the corresponding linear combinations of the parameters.

Bonferroni correction was used to control for type I error, and a P value below $.05 \div 15 = .003$ was considered statistically significant. All comparisons were two tailed. All analyses were performed on a personal computer (Proc Mixed; SAS Institute, Cary, NC).

RESULTS

Evaluation of Implanted VX2 Liver Tumor

All rabbits tolerated surgery for tumor implantation. After the rabbits were killed, the tumors were excised. They were found to be solitary spheres that measured 0.9–1.2 cm in diameter. No intrahepatic disseminated nodules or lung metastases were detected macroscopically. In three control rabbits, examination of hematoxylin-eosin–stained tumor sections showed poorly differentiated

Table 2
Radioactivity of Different Tissue 4 Days after Injection

Emulsion	Radioactivity (kBq/g) in Tissue		
	Liver	Tumor	Lung
Iodized oil ultrafluid			
Pure	21.01 ± 4.01	74.51 ± 7.10	19.75 ± 3.25
Small droplet			
Water-in-oil	29.60 ± 7.91	109.49 ± 25.50	3.72 ± 3.39
Oil-in-water	16.19 ± 1.82	80.22 ± 12.60	10.51 ± 1.18
Large droplet			
Water-in-oil	13.81 ± 4.72	141.07 ± 17.89	4.70 ± 2.31
Oil-in-water	22.23 ± 7.24	80.86 ± 11.70	5.57 ± 2.92
Iodized oil fluid			
Pure	20.03 ± 3.75	97.31 ± 12.64	19.48 ± 6.15
Large droplet			
Water-in-oil	15.39 ± 2.67	146.70 ± 10.74	6.27 ± 1.21
Oil-in-water	19.41 ± 5.06	99.35 ± 15.47	8.14 ± 2.49

* Data are mean ± standard error of the mean.

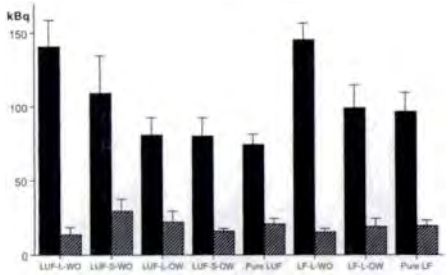

Figure 1. Radioactivity (kilobecquerel per gram of tissue) in tumor (black bars) and nontumorous (striped bars) liver 4 days after injection of pure iodized oil (Lipiodol) ultrafluid (*LUF*) and fluid (*LF*) and the six emulsions (*L* = large droplet, *S* = small droplet; *OW* = oil in water, *WO* = water in oil).

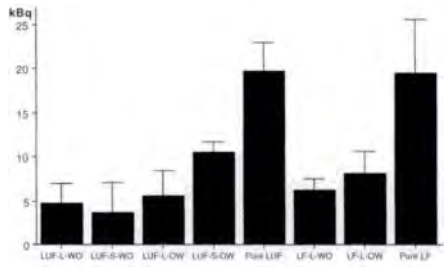

Figure 2. Radioactivity (kilobecquerel per gram of tissue) in lung 4 days after injection of pure iodized oil (Lipiodol) ultrafluid (*LUF*) and fluid (*LF*) and the six emulsions (*L* = large droplet, *S* = small droplet; *OW* = oil in water, *WO* = water in oil).

tumor without a surrounding capsule. The tumor had minimal focal necrosis and was sharply demarcated from the surrounding normal liver parenchyma.

Catheterization

Catheterization was not successful in two rabbits, owing to inadvertent dissection of the hepatic artery, which precluded injection of any sort. In another rabbit, the hepatic artery could not be catheterized selectively owing to anatomic variation. All rabbits injected with iodized oil or emulsions tolerated the substances well until they were killed.

Quantification of Radiolabeled Iodized Oil Uptake

The radioactivity doses (kilobecquerel per gram of tissue) received by the tumor, nontumorous liver, and the lung are shown in Table 2 and represented in Figures 1 and 2.

Tumor uptake of iodized oil fluid was significantly higher ($P < .0001$) with water-in-oil emulsions (both large- and small-droplet emulsions) than with pure iodized oil ultrafluid or oil-in-water emulsions (both large- and small-droplet emulsions). Among iodized oil ultrafluid water-in-oil emulsions, there was a trend toward a difference ($P = .0137$) in favor of large-droplet emulsions. Tumor uptake was significantly higher ($P < .001$) with iodized oil fluid water-in-oil large-droplet emulsions than with pure iodized oil fluid or iodized oil fluid oil-in-water emulsions.

Nontumorous liver uptake of iodized oil did not differ significantly with any of the products injected.

Lung uptake of iodized oil was significantly higher ($P < .003$) with pure iodized oil ultrafluid (19.75 kBq/g ± 3.25 [standard error of the mean]) than with any emulsion composed of iodized oil ultrafluid (range, 3.72–5.57 kBq/g; mean, 4.66 kBq/g), except for iodized oil ultrafluid oil-in-water small-droplet emulsions (10.51 kBq/g ± 1.18), which was not significantly different ($P = .011$) from results with pure iodized oil ultrafluid. Lung uptake of pure iodized oil fluid was significantly higher ($P < .003$) than lung uptake of any emulsion composed of iodized oil ultrafluid.

The ratio of tumor to nontumorous liver uptake of iodized oil (Table 3, Fig 3) was significantly higher ($P < .0001$) with iodized oil ultrafluid water-in-oil large-droplet emulsion (10.26 ± 2.88) than with pure iodized oil ultrafluid (3.68 ± 0.77) or with any other emulsion of iodized oil ultrafluid (range, 3.84–5.02; mean, 4.31). The ratio was significantly higher ($P < .003$) with iodized oil fluid water-in-oil large-droplet emulsion than with pure iodized oil fluid or with iodized oil fluid oil-in-water large-droplet emulsion.

The ratio of lung to lung-plus-liver uptake (Table 3) was significantly ($P < .003$) higher with pure iodized oil ultrafluid and pure iodized oil fluid (0.49 ± 0.04 and 0.48 ± 0.07, respectively) than with any emulsions (range, 0.09–0.31; mean, 0.23) except for iodized oil ultrafluid oil-in-water small-droplet emulsion, which had a ratio close to that of pure iodized oil (0.40 ± 0.04).

DISCUSSION

When injected into arteries, iodized oil had two major effects. First, it slowed arterial flow, owing to a temporary embolic effect. Second, it gave rise to preferential uptake and fixation by tumor. Because of the preferential uptake of iodized oil by hepatic tumors, CT enhanced with iodized oil is performed to evaluate the dissemination of hepatic tumors. Today, this technique remains one of the most sensitive means of evaluating distant spread of hepatocellular carcinoma (8,9). Recently I-131 iodized oil has been injected into the hepatic artery during interstitial radiation therapy in liver tumors, owing to its ability to target and remain preferentially in tumors. When iodized oil is injected into the hepatic artery, it is sometimes pure or sometimes mixed with other liquids (saline solution, contrast media, anticancer drugs). These mixtures of immiscible iodized oil and an aqueous liquid always produce emulsions. Some authors have used emulsions at CT enhanced with iodized oil or I-131 iodized oil therapy, and other authors (sometimes the same authors in later studies) have used pure iodized oil (7,10). To our knowledge, very little or imprecise information has been provided about how iodized oil is used, and provision of details regarding the formulation of the emulsions is an exception. Indeed, the direction (water in oil or oil in water), the granu-

lometry (size of the internal-phase droplets), and the proportion of each component are rarely provided. Moreover, reproduction of the emulsions is often difficult since the most common method to prepare them is the push-and-pull method through a three-way stopcock. An increase in the amount of iodized oil uptake by tumor is of interest in I-131 iodized oil interstitial radiation therapy or in CT enhanced with iodized oil, but to our knowledge no authors have attempted to increase this uptake in a manner other than hyperselective catheterization (11). In a previous study of the embolic effect of iodized oil, we demonstrated differences in intravascular behavior of iodized oil when pure iodized oil ultrafluid or various emulsions were injected intraarterially (12). Our observation of these differences prompted us to perform the present study, as we believed these differences seemed capable of inducing variations in iodized oil uptake by tumor.

Iodized oil ultrafluid is commonly used in clinical applications, whereas iodized oil fluid has been the subject of only a few studies, notably in kidney embolization (13). No significant differences were found in uptake of pure iodized oil ultrafluid or fluid or their emulsions in tumor, liver, and lung. Consequently, findings with iodized oil ultrafluid should remain the standard of reference, as ultrafluid is readily injected because of its lower viscosity.

Lung uptake of pure iodized oil ultrafluid or fluid was significantly higher than uptake of any of their emulsions except iodized oil ultrafluid oil-in-water small-droplet emulsion. The dose to the lung reported in the literature was 0%–46% in the study of Perring et al (14) and was 14%–25% in the study of Raoul et al (10). In our study, the ratio between uptake in the lung and in the lung plus liver was 49% for both pure iodized oil ultrafluid and fluid. The same ratio was 28% for emulsions of both iodized oil fluids and was 19% for all emulsions of iodized oil ultrafluid except the oil-in-water small-droplet emulsions, with which the ratio was 41%. Therefore, to minimize uptake of iodized oil in lung, emulsions (*other* than oil-in-water small-droplet emulsions) should be used instead of pure iodized oils for intraarterial injection. Such emulsions can be used when injecting I-131 iodized oil to minimize radiation to the lung, which may induce pulmonary fibrosis. Such emulsions could also be used in CT enhanced with iodized oil or chemoembolization to minimize potentially adverse effects to the lung,

Table 3
Ratio of Radioactivity per Gram of Tissue 4 Days after Injection

Emulsion	Tumor to Nontumorous Liver	Liver to Lung Plus Liver
Iodized oil ultrafluid		
Pure	3.68 ± 0.77	0.49 ± 0.04
Small droplet		
Water-in-oil	4.07 ± 1.73	0.09 ± 0.12
Oil-in-water	5.02 ± 0.79	0.40 ± 0.04
Large droplet		
Water-in-oil	10.26 ± 2.88	0.25 ± 0.08
Oil-in-water	3.84 ± 0.91	0.21 ± 0.08
Iodized oil fluid		
Pure	4.96 ± 0.92	0.48 ± 0.07
Large droplet		
Water-in-oil	9.53 ± 0.64	0.31 ± 0.14
Oil-in-water	5.38 ± 1.76	0.28 ± 0.09

* Data are mean ± standard error of the mean.

which have been rarely reported (15), to our knowledge. Interestingly, uptake of iodized oil in the lung was highest with the iodized oil ultrafluid oil-in-water small-droplet emulsion than with any other emulsion and was not significantly different from uptake of pure iodized oil in the lung. We previously demonstrated with in vivo microscopy that iodized oil ultrafluid oil-in-water small-droplet emulsions had a particular vascular behavior. Indeed, they provide the smallest droplets of iodized oil ultrafluid, which traverse tissues with a lower embolic effect than any other product (12). Cay et al demonstrated with in vivo microscopy that only these small (diameter, < 20 μm) emulsions were able to ensure passage of iodized oil into hypovascular liver metastases (16). Thus, it appears that such emulsions are capable of entering any liver tissues (healthy, neoplastic, hypovascular, or hypervascular), but they have a seemingly low embolic effect, tumor uptake is low, and they are, therefore, rapidly entrapped in the lung.

Tumor uptake of water-in-oil emulsions was significantly higher than tumor uptake of oil-in-water emulsions composed of either iodized oil ultrafluid or fluid. This difference is easily explained on the basis of results in our previous study (12), if it is accepted that arteries in tumor are larger than arteries in nontumorous liver. We found that iodized oil had a propensity to run through large vessels when the size of the oily emboli increased, and we found that water-in-oil emulsions provided the largest oily emboli, owing to their continuous phase of iodized oil. Tumor uptake of pure iodized oil ultrafluid and fluid

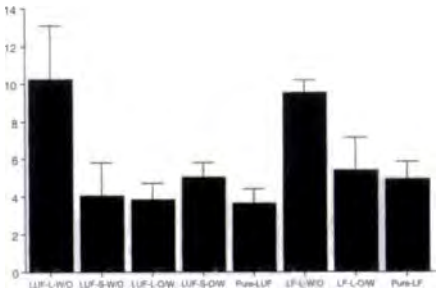

Figure 3. Ratio of radioactivity per gram of tissue in tumor to nontumorous liver 4 days after injection of pure iodized oil (Lipiodol) ultrafluid (*LUF*) and fluid (*LF*) and the six emulsions (*L* = large droplet, *S* = small droplet; *OW* = oil in water, *WO* = water in oil).

was significantly lower than tumor uptake of water-in-oil emulsions, although the pure iodized oil fluid or ultrafluid also provided large oily emboli. We lack a valid explanation for this except that even if the volume of iodized oil injected was always the same, the total injected volume was about half that for pure iodized oil compared with that of emulsions.

The ratio of iodized oil uptake between tumor and nontumorous liver showed a significant advantage with large-droplet water-in-oil emulsions (of either iodized oil ultrafluid or fluid) compared with any other product (iodized oil ultrafluid water-in-oil large-droplet emulsion, 10.26 ± 2.88; iodized oil fluid water-in-oil large-droplet emulsion, 9.53 ± 0.64 [all other products, range, 3.84–5.38, mean, 4.49]). This compared favorably with the result of 4.3 ± 3.6 reported by Raoul et al (10) in human hepatocellular carcinoma and with the results of 2.4 ± 0.7 and 3.1 reported by Raoul et al (10) and Perring et al (14), respectively, in human metastases.

Yoo et al (11) reported a higher ratio, but they performed hyperselective catheterization of the vessels feeding the tumor before they injected the I-131 iodized oil.

On the basis of results in this study, iodized oil ultrafluid water-in-oil large-droplet emulsion appears to be the most satisfactory product for use in I-131 iodized oil and CT enhanced with iodized oil because tumor uptake is high and lung uptake is limited. One drawback, however, is acquisition and validation of such emulsions with adequate radiation protection for use in I-131 iodized oil in clinical practice. Moreover, the larger the emulsions, the less stable they are, and the greater the need to prepare them on the spot.

The pharmacokinetic advantages of use of mixtures of iodized oil and anticancer drugs over use of the anticancer drugs alone when injected intraarterially have been reported in many studies (17–20). On the basis of results in this study, however, we cannot recommend use of a particular mixture of anticancer drug and iodized oil. Although high tumor uptake of iodized oil during chemoembolization has been described to be associated with a good clinical result (21,22), both the embolic effect and the preferential uptake of iodized oil by tumor can be involved in the pharmacokinetic benefit. Indeed, slowing the blood flow prolongs the dwell time of the drug within the tumor, and preferential uptake of iodized oil can be expected to increase the amount of drug directed at the tumor. In theory, the best emulsion would be one that combines the highest embolic effect with the best iodized oil uptake by the tumor, and thus large-droplet water-in-oil emulsions seem to fulfill these criteria, as we found in this study and previously (12). Other factors, however, probably play a critical role in drug targeting of tumors. Indeed, we found that large-droplet water-in-oil emulsions separate into a succession of pure iodized oil and pure drug when they reach vessels of the size of the suspended drug droplets (12), thus releasing the drug from iodized oil in proximal large (diameter, 70–100 μm) arteries soon after injection. Small-droplet water-in-oil emulsions, however, separate in more distal small (diameter, 20–30 μm) vessels, which are probably neoplastic, and thus provide improved targeting of the drug. Therefore, it is difficult to propose clear-cut recommendations about the type of emulsion to be used in chemoembolization. Performance of studies to investigate drug concentration in tumors after injection of various types of emulsions would help formulation of such recommendations.

On the basis of our results in this study and in previous studies, we wish to warn clinicians about use of small-droplet oil-in-water emulsions. Such emulsions generate a low embolic effect, a high lung uptake, and a low ratio of tumor to nontumorous liver uptake and therefore should not be used in intraarterial injection of iodized oil at CT enhanced with iodized oil, chemoembolization, or I-131 iodized oil therapy. Large-droplet water-in-oil emulsions provided the best uptake of iodized oil by tumor in an animal model, and these results have to be confirmed in humans. ■

Acknowledgments: We thank Patrice Ardouin (animal facilities, Institut Gustave Roussy) and Dominique Violot and Annick Lamand (Department of Radiophysics, Institut Gustave Roussy) for their help in this work. We thank Jean-Claude Saccavini from CIS Bio International Laboratories for providing I-125 iodized oil. We also thank Lorna Ste Ange for the linguistic revision of the manuscript for this article.

References

1. Nakakuma K, Tashiro S, Hiraoka T, Ogata K, Ootsuka K. Hepatocellular carcinoma and metastatic cancer detected by iodized oil. Radiology 1985; 154:15–17.
2. Yumoto Y, Jinno K, Tokuyama K, et al. Hepatocellular carcinoma detected by iodized oil. Radiology 1985; 154:19–24.
3. Takayasu K, Shima Y, Muramatsu Y, et al. Hepatocellular carcinoma: treatment with intraarterial iodized oil with and without chemotherapeutic agents. Radiology 1987; 162:345–351.
4. Konno T, Maeda H, Iwai K, Maki S, Tashiro S, Uchida M. Selective targeting of anticancer drug and simultaneous image enhancement in solid tumors by arterially administered lipid contrast medium. Cancer 1984; 54:2367–2374.
5. Roche A. Chemoembolization of liver malignancies. In: Ferrucci JT, Mathieu D, eds. Advances in hepatobiliary radiology. St Louis, Mo: Mosby, 1990; 295–305.
6. Iwai K, Maeda H, Konno T. Tumor targeting by arterial administration of lipids: rabbit model with VX2 carcinoma in the liver. Anticancer Res 1987; 7:321–328.
7. Raoul JL, Guyader D, Bretagne JF, et al. Randomized controlled trial for hepatocellular carcinoma with portal vein thrombosis: intra-arterial iodine-131-iodized oil versus medical support. J Nucl Med 1994; 35: 1782–1787.
8. Bruneton JN, Kerboul P, Grimaldi C, et al. Hepatic intraarterial Lipiodol: technique, semiologic patterns, and value for hepatic tumors. Gastrointest Radiol 1988; 13:45–51.
9. Ngan H. Lipiodol computerized tomography: how sensitive and specific is the technique in the diagnosis of hepatocellular carcinoma? Br J Radiol 1990; 63:771–775.
10. Raoul JL, Bourguet P, Bretagne JF, et al. Hepatic artery injection of I-131–labeled Lipiodol: biodistribution study results in patients with hepatocellular carcinoma and liver metastases. Radiology 1988; 168:541–545.
11. Yoo HS, Park CH, Lee JT, et al. Small hepatocellular carcinoma: high dose internal radiation therapy with superselective intra-arterial injection of I-131–labeled Lipiodol. Cancer Chemother Pharmacol 1994; 33(suppl):S128–S133.
12. de Baere T, Dufaux J, Roche A, et al. Circulatory alterations induced by intra-arterial injection of iodized oil and emulsions of iodized oil and doxorubicin: experimental study. Radiology 1995; 194:165–170.
13. Park J, Jeon S, Kang H, Im J, Han M, Kim C. Transcatheter renal arterial embolization with the mixture of ethanol and iodized oil (Lipiodol). Invest Radiol 1986; 21:577–580.
14. Perring S, Hind R, Fleming J, Birch S, Batty V, Taylor I. Dosimetric assessment of radiolabeled Lipiodol as a potential therapeutic agent in colorectal liver metastases using combined CT and SPECT. Nucl Med Commun 1994; 15:34–38.
15. Lorcher U, Peters J, Kollath J. Veranderungen der lunge und pleura nach chemoembolizton von lebertumoren mitmitomycin-Lipiodol. ROFO 1990; 152:569–573.
16. Cay O, Kruskal J, Thomas P, Clause ME. Targeting of different ethiodized oil–doxorubicin mixtures to hypervascular hepatic metastases with intraarterial and intraportal injections. JVIR 1996; 7:409-417.
17. Kawaguchi T, Fukushima S, Hayashi Y, Kaneko M, Nakano M. Selective accumulation of 3,5-dioc-tanoyl-5-fluoro-2-deoxyuridine (FdUrd-C8) and sustained release of its active metabolites in VX2 rabbit hepatoma following intraarterial administration of FdUrd-C8 solution in Lipiodol. Cancer Res 1988; 48:4179–4183.
18. Zhao Z, Ramirez LN, Simenauer N. Pharmacokinetics of intraarterial hepatic THP-Adriamycin-Lipiodol in rabbits with VX2 tumors. Regional Cancer Treat 1993; 4:213–217.
19. Raoul JL, Heresbach D, Bretagne JF, et al. Chemoembolization of hepatocellular carcinomas: a study of the biodistribution and pharmacokinetics of doxorubicin. Cancer 1992; 70:585–590.
20. Fukushima S, Kubota M, Kojima T, et al. Preparation and evaluation of two formulations: cisplatin suspension in Lipiodol and polylactic acid microspheres containing aclarubicin hydrochloride for hepatic arterial administration therapy for hepatocellular carcinoma. Regional Cancer Treat 1992; 2:36–39.
21. Van Beers B, Roche A, Cauquil P. Transcatheter arterial chemotherapy using doxorubicin, iodized oil, and Gelfoam embolization in hepatocellular carcinoma. Acta Radiol 1989; 30:415–418.
22. Imaeda T, Ymawaki Y, Seki M, et al. Lipiodol retention and massive necrosis after Lipiodol-chemoembolization of hepatocellular carcinoma: correlation between computed tomography and histopathology. Cardiovasc Intervent Radiol 1993; 16:209–213.