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Small hepatocellular carcinoma: high dose internal radiation therapy with superselective intra-arterial injection of I-131-labeled Lipiodol

Hyung Sik Yoo[1], Chan Hee Park[2], Jong Tae Lee[1], Ki Whang Kim[1], Chun Sik Yoon[1], Jung Ho Suh[1], Chang Yun Park[1], Byung Soo Kim[3], Heung Jai Choi[4], Kyong Sik Lee[5], Chan Il Park[6]

[1] Department of Radiology, Yonsei University College of Medicine, Seoul, Korea
[2] Division of Nuclear Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA
[3] Department of Cancer Center, Yonsei University College of Medicine, Seoul, Korea
[4] Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[5] Department of Surgery, Yonsei University College of Medicine, Seoul, Korea
[6] Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

Abstract. The aim of the present study was to deliver a high internal radiation dose to small hepatocellular carcinoma (HCC) lesions in an attempt to treat this disease. A total of 18 patients with HCC lesions measuring less than 4.5 cm in diameter (25 lesions) were treated with superselective intra-arterial injection of I-131-labeled Lipiodol (370–1,100 MBq in 3–5 ml) using a 5-F or coaxial catheter. All the lesions were nodular, multinodular, or hypervascular on pretreatment angiography. In all, 15 lesions that received over 180 Gy of cumulative radiation decreased in size in proportion to the Lipiodol retention on CT, and no pericapsular recurrence was found on angiography after 14–54 months of follow-up. In five patients who subsequently underwent surgery, 65% to 100% tumor necrosis was detected. No abnormal change in liver function tests or untoward clinical symptom of the lung, thyroid, or bone marrow was detected in patients who survived for more than 3 years after the treatment. Superselective high-dose internal radiation therapy of small HCC offers hope of treatment and long-term local control without complications.

Introduction

Lipiodol (Lipiodol Ultra-Fluide; Laboratoire Guerbert, France) is an ethyl ester of poppyseed oil fatty acids that contains 38% iodine by weight. It has been used as a therapeutic vehicle of chemotherapeutic agents [5, 14, 16] and, recently, radiolabeled iodine (I-131 Lipiodol) in the treatment of hepatocellular carcinoma (HCC) [4, 7, 11, 17].

The biodistribution and in vivo kinetics of intrahepatic I-131 Lipiodol injected into the hepatic artery revealed that there was a higher tumor-to-nontumor ratio of radioactivity and a longer effective half-life in the vascular HCCs than in the normal adjacent hepatic tissues [1, 7, 9, 13, 17]. Thus, the potential of internal radiotherapy delivered by this method has been fully appreciated, and therapeutic attempts have been applied to HCCs and metastatic tumors by I-131 Lipiodol injection at the level of the hepatic artery [1, 17, 18].

To assess the therapeutic usefulness of I-131 Lipiodol in small (<4.5 cm) HCCs by applying subsegmental intrahepatic arterial catheterization instead of hepatic artery injection, we studied the biodistribution characteristics of I-131 Lipiodol in this method. The efficacy of this treatment was evaluated by serial follow-up of the serum α-fetoprotein (AFP) level and by computed tomography (CT) and hepatic arteriography. Histopathologic examinations of resected specimens placed particular emphasis on the extent of tumor necrosis and the distribution of I-131 Lipiodol within the tumor.

Patients and methods.

Patients and lesions. Beginning in February 1987, a total of 25 small HCCs in 18 patients became the subjects of the present study. The longest diameter of the lesions ranged from 1.5 to 4.5 cm; that of 12 lesions was less than or equal to 3.0 cm, and that of 13 was greater than 3.1 cm. There were 14 men and 4 women whose age ranged from 44 to 72 years (mean, 58 ± 14 years). None had received any previous chemotherapy. Of the 18 patients, 14 had cirrhosis of the liver (histologically proven to be alcoholic in 2 cases and posthepatitis in 12). According to Child's classification criteria, 9 of these patients had Child's A disease, 3 had Child's B disease and 2 had Child's C disease. The diagnosis of HCC was established by ultrasonography-guided biopsy in 15 patients and by an elevated serum AFP level (more than 400 ng/ml) with abnormal diagnostic images in 3 patients. The serum AFP value in these patients was normal (<20 ng/ml) in 4 cases slightly increased (>400 ng/ml) in 8, and markedly increased (over 400 ng/ml) in 6. All the lesions were hypervascular, and there was no clinical or radiographic evidence of metastatic lesions in other organs. In all, 1 patient had 3 lesions, 5 patients had 2 lesions, and 12 patients had a single lesion. Among the 25 lesions, 6 had recurred after surgery, 3

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Correspondence to: Hyung Sik Yoo, Department of Radiology, Yonsei University College of Medicine, C. P. O. Box 8044, Seoul, Korea

were located close to the hilar area, and 6 were situated near the hepatic capsule and, thus, not suitable for percutaneous ethanol injection (PEI) therapy. Prior to the start of the therapy, informed consent was obtained from all the patients or their relatives after the therapeutic procedures had been fully explained.

Five patients who had a nodular lesion underwent surgical resection after treatment (between 4 and 12 weeks), and these patients were excluded from the evaluation of the therapeutic effect.

Administration of I-131 Lipiodol. Radioiodination of Lipiodol (I-131 Lipiodol) was achieved by a simple exchange method. The details of this method have been reported elsewhere [7, 17, 18]. I-131 Lipiodol was prepared to have a specific activity concentration of 185–280 MBq/ml with a labeling efficiency of 99%. Angiography was performed at the level of the hepatic artery using a 5-F catheter (Terumo Radiofocus soft catheter), and the location, vascularity, and feeding vessels of the tumor were evaluated. A therapeutic dose of 370–1,110 MBq of I-131 Lipiodol (10–30 mCi in 1.5–6.0 ml) was injected into the subsegmental hepatic arteries that feed the tumor by means of a 5-F catheter or a coaxial infusion system (Tracker-18, target therapeutic; S-P catheter; Terumo). The dose and volume to be injected were determined on the basis of the CT measurement of size and the vascularity as shown by hepatic arteriography. Slow infusion was performed either manually or with an automatic injection syringe. Immediately after completion of the I-131 Lipiodol infusion, plain abdominal radiographs of the liver were taken to confirm homogeneous distribution of the injected volume. Lugol's solution was prescribed for the patients to block thyroid uptake of free radioiodine; this was ingested on the day before the infusion and for 3 days afterward. The patients were isolated for a period ranging from 3 days to 1 week in a private room for the purpose of radiation protection.

Biodistribution and dosimetry. After the injection, scintigraphic imaging was carried out on days 1, 3, 5, 7, 14, and 21. The biodistribution indices (ratio of activity between the liver and lung and between tumorous and nontumorous hepatic areas) and the effective half-lives in the tumor, liver, and lungs were measured over the region of interest (ROI) drawn on the single-photon-emission computed tomography (SPECT) images (transverse, sagittal, and coronal) or on the anterior and posterior views of gamma-camera images. The cumulative radiation dose for each tumor was calculated on the basis of Quimby's equation and an MIRD table:

$$\text{Dose to the tumor (cGy)} = 73.8 \times E\beta \times Te \times Ao/M + 0.0346 \times \Gamma \times Te \times G \times Ao/M,$$

where $E\beta$ is the average beta energy of I-131 (MeV), Te is the effective half-life in the tumor (days), Γ is the specific gamma-ray constant (R/mCi-h at 1 cm), Ao is the initial activity (μCi), M is the tumor mass (g), and G is the geometric factor (cm). For spherical objects, G is estimated from $3\ \pi R$ (R<10), where R is the tumor radius expressed in centimeters. The tumor mass (M) was determined from the CT scans, and dosimetry of the nontumorous hepatic area and lungs was measured as described previously [7, 17, 18].

Initial and follow-up studies. The baseline studies performed before treatment included hematologic tests, serum AFP, and liver function tests (LFTs). The size of the tumor was measured by CT by multiplying the two largest perpendicular diameters of the largest lesion.

Serial measurements of the serum AFP and LFTs (at 1- or 2-month intervals), sizing of the tumor by CT slices at a similar scanning level (at 2- or 3-month intervals), and hepatic arteriography (at 3- or 6-month intervals) were performed for the follow-up studies.

The therapeutic effects were evaluated on the basis of the sequential changes in the serum AFP level and the tumor size by means of CT. The reduction rate of the tumor was measured as follows: Percentage reduction in mass (%) = (pretreatment product of two largest diameters) – (posttreatment product of two largest diameters)/(pretreatment product of two largest diameters) ×100.

A "response" to the therapy was defined as shrinkage of the tumor on the CT scan, a decrease in the serum AFP level, and the absence of pericapsular tumor vessels on hepatic arteriography for at least 6 months after the treatment.

Pathology studies. Five patients underwent surgical resection (hepatic subsegmentectomy in four cases and hepatic lobectomy in one case) 4–12 weeks later for evaluation of the therapeutic effect on the tumors. The resected hepatic tissues were cut into 1-cm-thick slices. One slice was frozen immediately, and the others were immersed in 10% neutral formalin. Every slice that passed through the center of the global mass was cut into 3- × 1-cm blocks after the exact topography of the slice with the tumor had been sketched on transparent paper for mapping. Sections were made of the formalin-fixed blocks for hematoxylin-eosin and oil-red-O staining. Areas of necrosis were marked directly on the glass slides as accurately as possible. The area of each necrotic portion was mapped, and the total areas of viable tissue and necrotic tumor tissue in the slice were measured. Light microscopic examination was performed, with particular attention being paid to the distribution of Lipiodol in the HCC lesions.

Results

Subsegmental intrahepatic arterial injections were made through the right anterior-superior artery (nine lesions), right posterior-inferior artery (eight lesions), right-anterior-inferior artery (four lesions), right posterior-superior artery (two lesions), and left lateral segmental artery (two lesions). Selective retention of the I-131 Lipiodol is seen as an area of markedly high density in the tumor on hepatic arteriograms and CTs. Gamma-camera images demonstrated high radioactivity confined in the tumor and slight radioactivity in both lungs.

The effective half-life of the I-131 in the tumor ranged from 4.5 to 6.5 days, whereas it ranged from 3.5 to 4.5 days in the normal hepatic tissues. The ratio of radioactivity between the tumor and the nontumorous liver was 9–22:1 (15:1 on average). The mean calculated radiation dose delivered to the tumor was 183 ± 35 Gy (median, 168 Gy) as compared with 5.0 ± 2.2 Gy (median, 4.5 GY) delivered to the nontumorous liver and 3.0 ± 1.7 Gy (median, 2.5 Gy) delivered to the lungs.

The serum AFP value was monitored in eight patients whose levels were higher than 200 ng/ml before the treatment. In six of the eight patients, the level dropped rapidly between weeks 2 and 8 after treatment.

Table 1. Response rate according to size of tumor

Size of tumor (cm)	No. of lesions	Reduction rate (%)			Responding lesions	Responding rate (%)
		<25	26–49	>50		
1. 5–2.5	7	3	2	2	7	100
2. 6–3.5	7	0	4	1	5	71
3. 6–4.5	6	0	2	1	3	50

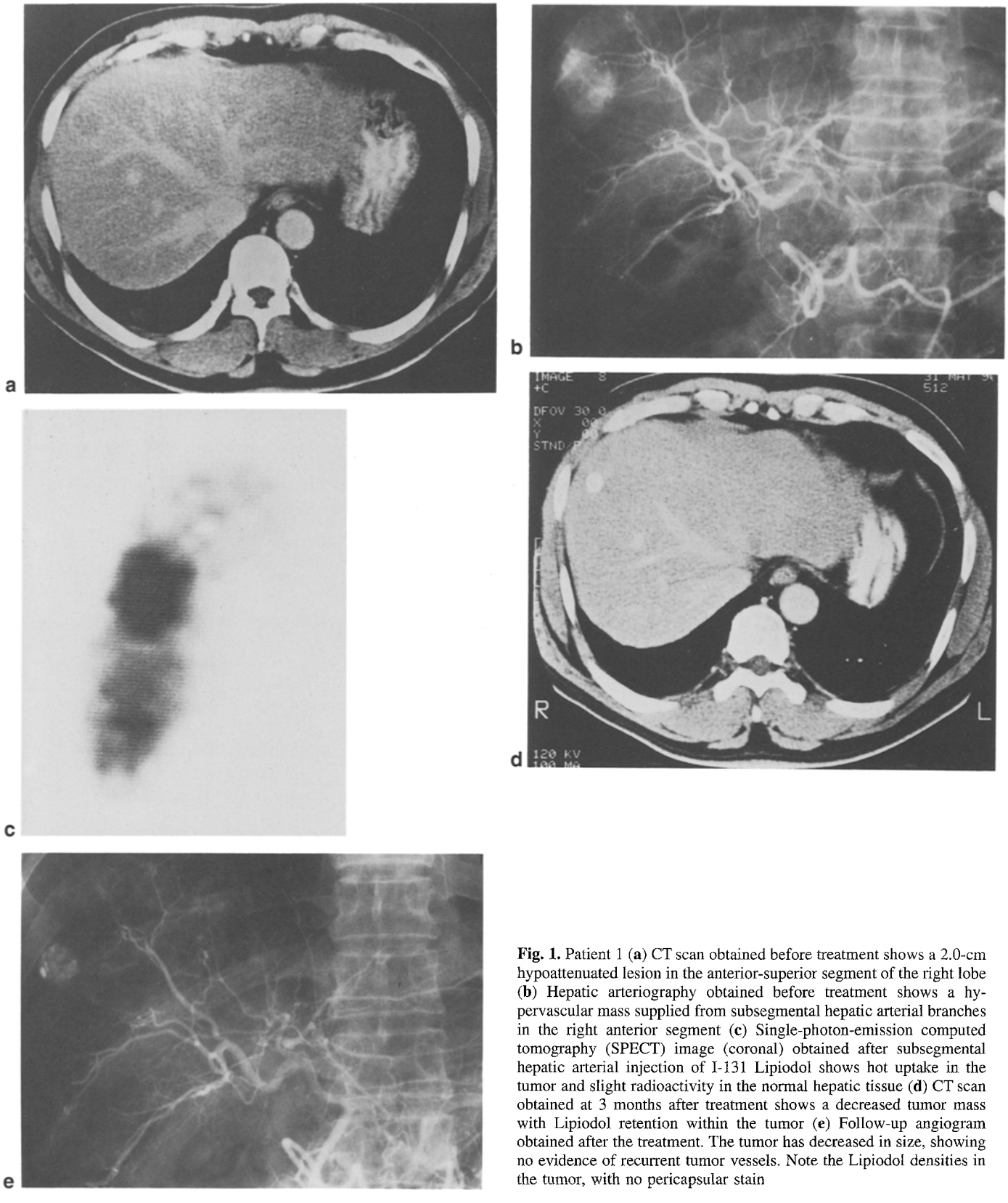

Fig. 1. Patient 1 (**a**) CT scan obtained before treatment shows a 2.0-cm hypoattenuated lesion in the anterior-superior segment of the right lobe (**b**) Hepatic arteriography obtained before treatment shows a hypervascular mass supplied from subsegmental hepatic arterial branches in the right anterior segment (**c**) Single-photon-emission computed tomography (SPECT) image (coronal) obtained after subsegmental hepatic arterial injection of I-131 Lipiodol shows hot uptake in the tumor and slight radioactivity in the normal hepatic tissue (**d**) CT scan obtained at 3 months after treatment shows a decreased tumor mass with Lipiodol retention within the tumor (**e**) Follow-up angiogram obtained after the treatment. The tumor has decreased in size, showing no evidence of recurrent tumor vessels. Note the Lipiodol densities in the tumor, with no pericapsular stain

During the follow-up period of up to 54 months, 15 of 20 lesions (75%) showed a reduction in size after the treatment (Table 1). The responding lesions were characterized by selective, high radioactivity of I-131 Lipiodol in the tumor on gamma-camera images, shrinkage of the tumor with Lipiodol retention on CTs, and the absence of pericapsular recurrence on hepatic arteriograms (Fig. 1). The reduction in size ranged from 11% to 75% (median, 36%). Five lesions showed tumor growth within 9 months after the treatment. Two of five lesions that became larger

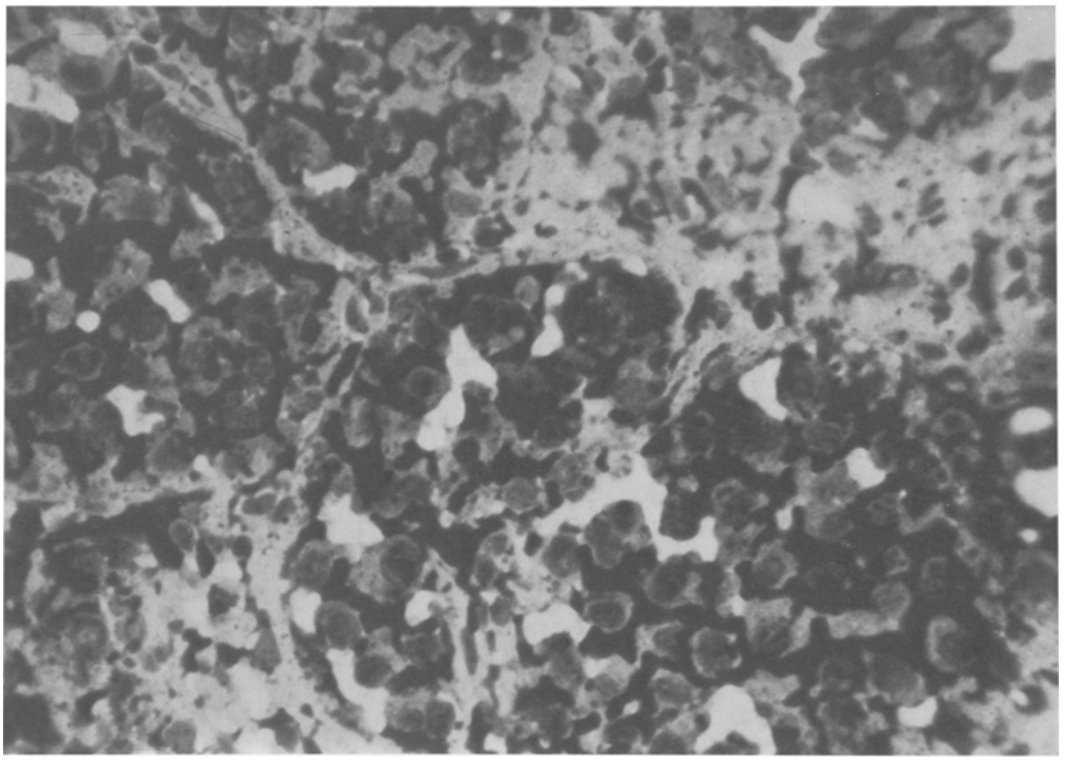

Fig. 2. Photomicrograph (× 400, oil-red-O stain) showing Lipiodol surrounding the membranes of the tumor cells, yielding a honeycomb-like appearance

Table 2. Findings in five lesions of HCC after surgical resection

Patient	Age (years)	Initial size of tumor (cm)	Final size of tumor (cm)	Time until surgery (weeks)	Radiation dose of tumor (GY)	Tumor necrosis in resected specimen (%)
1	46/M	4.0 × 4.0	4.0 × 4.0	4	65	63
2	58/M	2.0 × 2.0	2.0 × 2.0	4	78	65
3	48/M	3.5 × 3.5	3.0 × 3.0	8	120	78
4	53/F	2.5 × 2.5	2.2 × 2.2	12	165	100
5	56/M	1.8 × 1.8	1.5 × 1.5	12	180	100

showed rapid clearance of the intratumoral I-131 Lipiodol, probably due to significant arteriovenous shunts within the tumor. The remaining three lesions showed an inhomogeneous distribution of I-131 Lipiodol within the tumor, presumably due to an inadequate amount having been injected.

Patients complained of slight pain in the area of the liver, and temporary abdominal pain and mild fever developed within a few days after the infusion. These symptoms were transient and well tolerated by the patients. LFTs revealed a transient elevation of serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels, which returned to normal levels after a few days. There was no abnormal change in the bilirubin, alkaline phosphatase, or blood urea nitrogen levels. Of the 13 patients evaluated, 8 are alive and well at the time of this writing, at more than 1 year after the initial treatment, without having developed any complications of the thyroid, lung, GI tract, or bone marrow. Two patients developed portal vein thrombi by the tumor, and three developed new tumor masses in the other lobe of the liver during the follow-up period.

The resected lesions were nodular and measured 1.8–4.0 cm in the largest diameter. Soft-tissue radiography of the surgical specimens demonstrated that I-131 Lipiodol was significantly deposited in the tumor vessels. Endothelial wall thickening of the tumor vessels was apparent, and necrotic areas were replaced by granulation tissues. Oil-red-O staining showed that the individual tumor cells were surrounded on their surface by I-131 Lipiodol, resulting in a honeycomb-like appearance (Fig. 2).

Completely hemorrhagic and coagulative necrosis was found in two lesions (1.8 × 1.8 cm; 2.5 × 2.5 cm), and 63%–78% tumor necrosis was found in the other three lesions (Table 2).

Discussion

The lipid lymphographic agent Lipiodol has been found to remain selectively in tumor tissues of the liver for a long time when injected into the hepatic artery [5]. On the basis of this finding, a therapeutic approach for small HCCs has been developed using antitumor drug emulsions with or without Gelfoam embolization. However, the results obtained in terms of the therapeutic effects on resected specimens indicated that Lipiodol infusion alone was not effective in causing tumor necrosis as compared with the Gelfoam embolization group [14, 16]. Because Lipiodol contains stable iodine 127, labeling of Lipiodol with radioactive I-131 can be achieved by a simple radioisotopic exchange method [4, 11].

Studies of the biodistribution and in vivo kinetics of I-131 Lipiodol delivered by hepatic arterial injection to patients with HCC have shown: (a) an effective half-life of 4–6 days in tumors, which is longer than that observed in the adjacent hepatic tissues and lungs; (b) 10%–15% localization of the injected dose within the HCC; (c) a tumor (T)-to-nontumor (NT) activity ratio (T/NT) of 4.3 ± 3.6; (d) initially increased activity in the lungs, which clears with a 5-day effective half-life; and (e) urinary excretion (30%–50% of the delivered dose of I-131 over 8 days) and biliary excretion (3% over 5 days) [7, 9, 13, 17].

Dosimetry studies on HCCs after injection at the level of the hepatic artery have been performed by several researchers [4, 7, 9, 13]. When 1 mCi (37 MBq) of I-131 Ethiodol is injected via the hepatic artery to a 4-cm-diameter tumor, the estimated dose delivered to the tumor is 239 rad, with 31 rad being delivered to the liver; 22 rad, to the lungs; and 1.9 rad, to the total body. Thus, 35 mCi (1,295 MBq) of activity is necessary for the delivery of 100 Gy to a 4-cm-sized vascular HCC, which also delivers 5.9 Gy to the lungs and 139 Gy to the normal adjacent hepatic tissues.

To deliver an even higher radiation dose to the tumor and to decrease the radiation dose to the normal hepatic tissues and lungs, superselective catheterization with the use of a flexible catheter is necessary. Small HCCs are usually supplied by tumor-feeding vessels that originate from the subsegmental branches. Subsegmental hepatic arterial catheterization can be performed through the right anterior-superior, right anterior-inferior, right posterior-inferior, left medial, and left lateral ventral branches without difficulty via a coaxial catheter system when the vessels are not tortuous. However, the left lateral dorsal, right posterior-superior, and caudate lobe branches cannot be easily cannulated due to their acute, angulated courses. In cases of advanced cirrhosis of the liver, it is not easy to pass a guidewire through the tortuous vessels.

In the current study, when I-131 Lipiodol was injected into a subsegmental hepatic artery under superselective catheterization, a higher T/NT liver ratio and a lower tumor-to-lung ratio were obtained in comparison with the method used by other investigators [9, 13]. Under superselective catheterization, tumors measuring less than 4.0 cm in diameter can receive an average dose of 140 Gy, with less than 2.5 Gy being delivered to the lungs and 4.5 Gy being delivered to the normal adjacent hepatic tissues. Thus, superselective catheterization is essential for delivering a higher dose to the tumor and keeping the radiation doses to the normal tissues safe and tolerable.

Recently, we reported on the interaction between Lipiodol and human HCC cell lines in vitro. Lipiodol was noted in the cytoplasm of the tumor cells as a globular lipid and on the cell surface as a nonglobular lipid that was firmly attached to the tumor cell membrane [3, 12].

The prolonged retention time of I-131 Lipiodol in the tumor may cause an increase in the adhesion of I-131 Lipiodol around the tumor cell membranes, which leads to destruction of the tumor cells due to its beta radiation. If one could label Lipiodol with I-125, I-125 Lipiodol might be more effective than I-131 Lipiodol since the Anger electrons from I-125 would be effective in this situation. In our histology studies, deposition of Lipiodol in the fine tumor vessels was obvious, and narrowing of the vascular lumens was observed, which may be induced by radiation vasculitis. Thus, the I-131 Lipiodol surrounding the tumor cell membranes and the vascular obstruction of fine tumor vessels due to radiation fibrosis may be responsible for the tumor necrosis.

Lipiodol may enter the portal vein through an arterioportal communication after pooling in the sinusoids. It is necessary to inject a sufficient volume of I-131 Lipiodol into the tumor-bearing hepatic tissue until dense opacification of the tumor and the regional portal vein radicles appears, since small HCCs are generally fed by diffusion from the sinusoids and may be supplied by the portal vein branches [15]. If the tumor shows rapid clearance of intratumoral I-131 Lipiodol due to arteriovenous shunts, it is necessary to occlude the tumor-feeding vessels with gelatin sponge particles or Ivalon particles for peripheral embolization. For the observation of I-131 Lipiodol inside tumors, plain abdominal radiography and CT scans can be used. However, to assess the response of the tumor, it is necessary to perform hepatic arteriography because plain abdominal radiography and CT scans may miss the washed-out I-131 Lipiodol in the peripheral portion of the tumor, thereby underestimating the size of the tumor during the follow-up studies.

The safe levels for radiation doses to the liver and lungs with internally delivered radionuclides remain unclear [8, 10]. Liver necrosis was found to occur at more than 120 Gy in dogs injected with colloidal potassium-32 chromic phosphate, but the delivery of 30 Gy internally in humans did not cause any side effect [2, 6].

Bretagne et al. [1] treated widespread HCCs with a high dose of I-131 Lipiodol (25–65 mCi, 900–2,400 MBq in 3 ml) injected into the hepatic artery. The calculated radiation dose was 12.5–70 Gy for the tumor, 2–15 Gy for the nontumorous liver, and less than 2.5 Gy for the lungs. No side effect or abnormality in pulmonary function or bone marrow depression was noted.

In the current study, there was no demonstrable radioactivity in the spleen, thyroid, or bone marrow. No significant abnormal change in liver function or untoward clinical symptom related to the lung, thyroid, or bone marrow was detected in these patients, who were followed for more than 2 years [19].

In summary, the present study suggests the following advantages:

1. A high tumor dose can be delivered with a single superselective injection, enabling tumor necrosis, without hazard to the normal parenchyma of the liver or lungs.
2. Multinodular HCCs or recurrent tumors after hepatic surgery can be treated by selective subsegmental arterial infusion.
3. Deep-seated tumors and peripheral tumors that are unsuitable for PEI therapy can be treated by this method.
4. Additional injections are possible since the tumor-feeding vessels are preserved.

The limitations of this treatment method appear to be that the tumor has to be hypervascular, without arteriovenous shunts, and homogeneous distribution of I-131 Lipiodol within the tumor must be performed under superselective catheterization.

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